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ANTIVIRAL DRUGS ADVISORY COMMITTEE

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C O N T E N T S

Epivir-HBV (lamivudine tablets and oral solution)
Glaxo Wellcome, Incorporated,
for treatment of chronic hepatitis B

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P R O C E E D I N G S

(8:30 a.m.)

DR. HAMMER: Good morning. I'd like to open today's session of the Antiviral Drugs Advisory Committee meeting.

Today we are happy to welcome Glaxo Wellcome, the sponsor, of lamivudine which we're going to consider for the treatment of chronic hepatitis B, and we will have, I think, a very interesting day discussing this drug and this issue.

I'd like to start by having the members and guests of the committee and members of the agency introduce themselves. I'll start on my right with Dr. Jolson.

DR. JOLSON: Good morning. I'm Heidi Jolson, Director of the Division of Antiviral Drug Products.

DR. STYRT: Barbara Styrt, medical officer, Division of Antiviral Drug Products.

MS. KUKICH: Stanka Kukich, acting medical team leader.

DR. SOON: Greg Soon, statistical reviewer.

DR. MASUR: Henry Masur from the Clinical Center, NIH.

DR. EL-SADR: Wafaa El-Sadr, Harlem Hospital, New York.

DR. DIAZ: Pamela Diaz, Chicago Department of

1 Public Health.

2 MS. STOVER: Rhonda Stover, FDA.

3 DR. HAMMER: Scott Hammer from the Beth Israel
4 Deaconess Medical Center and Harvard Medical School in
5 Boston.

6 DR. HAMILTON: John Hamilton, Division of
7 Infectious Diseases at Duke University.

8 DR. YOGEV: Ram Yogev, Division of Infectious
9 Diseases, Children's Memorial Hospital, Chicago.

10 DR. SO: Sam So, Stanford University, Director
11 of the Stanford Asian Liver Center.

12 DR. LEE: Sam Lee, hepatologist from the
13 University of Calgary, Canada.

14 MS. MELPOLDER: I'm Jackie Melpolder. I'm the
15 patient rep and also work at the Clinical Center at NIH.

16 DR. FLETCHER: Courtney Fletcher from the
17 Department of Clinical Pharmacology at the University of
18 Minnesota as a consumer rep.

19 DR. HAMMER: Thank you.

20 I'd like to turn to Rhonda Stover now who will
21 read the conflict of interest statement.

22 MS. STOVER: The following announcement
23 addresses the issue of conflict of interest with regard to
24 this meeting and is made a part of the record to preclude
25 even the appearance of such at this meeting.

1 Based on the submitted agenda for the meeting
2 and all financial interests reported by the participants,
3 it has been determined that all interests in firms
4 regulated by the Center for Drug Evaluation and Research,
5 which have been reported by the participants, present no
6 potential for a conflict of interest at this meeting with
7 the following exceptions.

8 In accordance with the provisions of 18 United
9 States Code 208(b)(3), full waivers have been granted to
10 Dr. Hamilton, Dr. Masur, Dr. Hammer, Dr. El-Sadr, and Dr.
11 Feinberg. A copy of these waiver statements may be
12 obtained by submitting a written request to the FDA's
13 Freedom of Information Office, room 12A-30 of the Parklawn
14 Building.

15 With respect to FDA's invited guests, there are
16 reported involvements which we believe should be made
17 public to allow the participants to objectively evaluate
18 their comments.

19 Dr. Ram Yogev would like to disclose that Glaxo
20 Wellcome is providing funding for a study of amprenavir in
21 pediatric patients.

22 Dr. Courtney Fletcher is the principal
23 investigator in a Glaxo Wellcome funded study of
24 antiretroviral therapy. Glaxo Wellcome provides Retrovir
25 and lamivudine for the study.

1 Lastly Dr. Maria Sjogren would like to disclose
2 that she is a co-investigator in a protocol using
3 lamivudine for renal disease in patients with chronic
4 hepatitis B. The study is supported by Department of
5 Defense funds. No pharmaceutical company support is
6 received.

7 In the event that the discussions involve any
8 other products or firms not already on the agenda for which
9 an FDA participant has a financial interest, the
10 participants are aware of the need to exclude themselves
11 from such involvement and their exclusion will be noted for
12 the record.

13 With respect to all other participants, we ask
14 in the interest of fairness that they address any current
15 or previous involvement with any firm whose products they
16 may wish to comment upon.

17 DR. HAMMER: Thank you.

18 I'd like to turn now to the Director of the
19 division, Heidi Jolson.

20 DR. JOLSON: Thank you, Dr. Hammer, and good
21 morning, ladies and gentlemen.

22 First I'd like to welcome our returning
23 advisory committee members and to also offer our sincere
24 thanks to today's consultants for joining us for this
25 meeting. I know several of them traveled quite a long

1 distance to be here today.

2 The division would also like to acknowledge
3 Glaxo Wellcome for their willingness to share their data
4 today. I believe that we in the division well recognize
5 that the design and conduct of clinical trials for
6 hepatitis therapies are particularly challenging. I think
7 that will be evident today. In this regard, the sponsor's
8 efforts in conducting this large development program for
9 their already-marketed product, lamivudine, should be
10 acknowledged.

11 Additionally, the agency appreciates the
12 participation of the patients in these trials. Their
13 participation has significantly contributed to the
14 understanding of the safety and efficacy of this therapy.

15 In the next few moments, I'd like to share my
16 perspective on today's meeting.

17 1998 has been an important year of progress for
18 treatment of chronic hepatitis B and C. Earlier this year
19 in May, this committee met to discuss the first application
20 for a nucleoside analog used in combination with alfa
21 interferon to treat relapse patients with hepatitis C.
22 Rabavirin, in combination with interferon, was approved in
23 June of this year. Today we meet to discuss an application
24 for the approved nucleoside analog lamivudine, the first
25 oral and the first non-interferon therapy for chronic

1 hepatitis B treatment. Investigation of the safety and
2 efficacy of this class of drugs represents an important
3 step in development of new treatment options for patients
4 living with this serious disease.

5 Today's meeting is also an opportunity to
6 emphasize many of the challenges ahead in this therapeutic
7 area. As will become evident in today's presentations,
8 drug development for hepatitis is particularly complex and
9 many questions remained unanswered. For example, today
10 will be the first opportunity for this particular committee
11 to discuss the clinical significance of serologic and
12 virologic changes in patients with chronic hepatitis B.

13 Ironically, it has been almost three years when
14 this committee was asked to address an analogous question
15 when the original NDA for lamivudine for HIV was presented.
16 At that time, change in HIV RNA was a newly available
17 surrogate endpoint in pivotal trials of HIV therapeutics.
18 As HIV treatment and trial designs have evolved
19 dramatically over the past several years, we anticipate
20 that our knowledge about treatment of chronic hepatitis
21 will also evolve in the years ahead.

22 We hope to make clear from today's
23 presentations that many issues in drug development still
24 need to be addressed to optimize use of current and future
25 therapies for this disease. These issues include the need

1 for targeting the appropriate patient populations for
2 treatment, establishing the optimal treatment durations,
3 determining the implications of viral resistance, and
4 importantly demonstrating the clinical benefit of drug
5 therapy.

6 As always, we look forward to and appreciate
7 your guidance on these and other issues that we will be
8 raised today. Thank you.

9 DR. HAMMER: Thank you very much.

10 I'd like to call on Dr. Marc Rubin who will
11 introduce the sponsor's presentation.

12 DR. RUBIN: Thank you. Good morning.

13 Over the next few minutes, I'm going to give
14 you a very brief overview of the clinical development
15 program for lamivudine for hepatitis B, and then Dr. Nat
16 Brown is going to take a bit longer to review some of the
17 specific components of that program.

18 This has been a very high priority for us at
19 Glaxo Wellcome because hepatitis B is a very important
20 disease. Worldwide it is one of the top 10 causes of
21 death. The CDC estimates that there are 300 million or so
22 people that are infected with hepatitis B worldwide. 75
23 percent of those are in Asia, and in fact about half of
24 them are in China specifically. It is estimated that
25 between a quarter and 40 percent of those individuals will

1 | die either of hepatitis or of hepatitis B related
2 | complications.

3 | Hepatitis B is also a significant concern in
4 | the United States where there are a little over a million
5 | individuals infected with the virus, and it is estimated
6 | that over the next year, there will be 17,000
7 | hospitalizations in the U.S. and over 5,000 deaths due to
8 | hepatitis B.

9 | Interestingly, while we typically think of the
10 | disease in Asia as being transmitted in the perinatal
11 | period and the disease in the western world as being
12 | transmitted horizontally, in fact even in the United
13 | States, up to 30 percent of people who have hepatitis B
14 | have acquired it in the perinatal period.

15 | Well, somewhat analogous to HIV, hepatitis B is
16 | a disease that's driven by viral replication. Accordingly,
17 | we believe that the main goal of therapy is to produce
18 | sustained reduction in viral load ideally before advanced
19 | disease sets in. Although it's difficult to actually show
20 | this in short-term clinical trials, I think it's logical to
21 | assume and we believe that if we can achieve longer-term
22 | reduction in viral load relatively early on, we can perhaps
23 | prevent the chronic sequelae of hepatitis B, particularly
24 | cirrhosis and hepatocellular carcinoma.

25 | With hepatitis B, there are really two ways to

1 achieve a reduction or longer-term reduction in viral load.
2 The first is to use an agent that's associated with
3 seroconversion which achieves reduction in viral load, and
4 that of course, happens with interferon. As we will also
5 see, that occurs with lamivudine.

6 The second, and somewhat analogous to HIV, is
7 to continue potent antiviral therapy to sustain that drop
8 in the viral load.

9 Interferon alfa now is the only approved
10 therapy. It's given by injection for up to six months. It
11 is, of course, associated with an increase in loss of HBe
12 antigen compared to those that don't receive it. Many
13 patients don't respond to interferon. The histologic
14 benefit is essentially limited to those patients who do
15 achieve long-term drops in viral load, signaled by HBe
16 antigen loss and seroconversion. It's injectable. It does
17 have a certain number of adverse reactions that overall
18 limit access and effectiveness of the therapy.

19 This is a map that just reviews the locations
20 of the clinical programs that Glaxo Wellcome has undertaken
21 with lamivudine and hepatitis B. It's a global disease
22 obviously, and this has been a truly global program for us.
23 So, we've had ongoing parallel programs, of course, in
24 North America and in Europe, but importantly, a large focus
25 of the program has also been in Asia.

1 The data that is in the NDA that you have
2 reviewed then comes from patients in trials from all of
3 these countries. We feel it's extensive. There are 21
4 phase I and phase II trials, enrolling just over 500
5 patients. There are four principal phase III trials, and
6 Dr. Brown will review the safety and efficacy from those
7 trials that have enrolled just under a thousand patients.
8 In addition, there are about 4,000 patients enrolled in a
9 variety of other controlled and uncontrolled trials and a
10 large compassionate use program as well.

11 So, the key features of lamivudine, we believe,
12 that are supported by the data are, first, that it does
13 offer the first oral therapy for chronic hepatitis B.
14 You'll see that it reduces hepatic necroinflammatory
15 activity in the majority of patients, and it also retards
16 the progression of fibrosis. We see enhanced HBe antigen
17 seroconversion, better than is seen with placebo and in a
18 similar range to that seen with interferon. We see an
19 increased frequency of ALT normalization and overall a
20 quite favorable safety profile.

21 We believe that the data will support then our
22 proposed indication for Epivir-HBV for the treatment of
23 chronic hepatitis B associated with evidence of hepatitis B
24 viral replication and with liver inflammation.

25 And I will turn over the podium to Dr. Brown.

1 DR. BROWN: Thanks, Marc. It's a pleasure to
2 be here today before the committee and its consultants and
3 agency staff. Nearly four years ago, we met with members
4 of the committee and agency staff to discuss the principal
5 endpoints and designs of hepatitis B trials, and I'm
6 pleased to be able to present the results of the planned
7 studies today from our principal phase III controlled
8 studies and other data as well.

9 A brief overview of my talk. Two slides on
10 disease-related background, two slides on some of the key
11 features of the preclinical aspects of lamivudine. And as
12 Marc mentioned, today I'll be concentrating especially on
13 the clinical data from the four controlled studies, but we
14 will review the key findings with regard to clinical
15 pharmacology for lamivudine in hepatitis B patients and
16 also briefly review data from other studies.

17 Hepatitis B virus is a quite small DNA virus, a
18 small genome with overlapping reading frames, four
19 principal genes. The hepatitis B surface antigen gene
20 encodes the envelope glycoprotein. The core antigen gene
21 encodes the capsid proteins comprising nucleocapsid shell
22 within the enveloped Dane particle. The hepatitis B
23 polymerase also has a reverse transcription function, as
24 most people here are aware. Polymerase here is illustrated
25 as attached to a DNA strand within the viral particle.

1 Inside cells the virus makes an X protein which can
2 function has a transcriptional transactivator, but the role
3 in the viral life cycle is essentially poorly understood.

4 An important facet of this virus is that the
5 first DNA template is replicated from an RNA transcript, so
6 there's a reverse transcription step which makes the
7 reverse transcriptase activity of the polymerase a
8 potential target for antiviral therapy just as for
9 retroviruses.

10 Now, the envelope glycoprotein, the surface
11 antigen, is produced in very large quantities in vast molar
12 excess, and it's quite easy to detect in blood. It self-
13 assembles into spherical and filamentous particles, and
14 therefore is used as the primary marker of infection with
15 this virus. It's very easy to detect surface antigen in
16 blood. It's present in such vast excess that it can be
17 detected often in the absence of appreciable levels of
18 viral replication, and as Marc mentioned, the level of
19 virus replication appears to be quite important to the
20 chances for disease progression. So, importantly, we also
21 measure measures of viral replication, serologic measures,
22 such as e antigen, which correlates with high viral
23 replication, and DNA levels as well. In the 1970s and
24 1980s, polymerase levels were often mentioned, but DNA
25 assays have largely replaced those.

1 The clinical course of chronic hepatitis B
2 virus infection is quite variable. Chronic infection with
3 the virus is generally defined worldwide as presence of
4 detectable serum surface antigen for 6 months or more in
5 the clinic. This kind of chronic infection has a very
6 broad range of outcomes, but importantly the primary
7 clinical sequelae of this disease and the primary cause of
8 death is liver disease. So, this does differ in some
9 respects from HIV which is obviously a multi-organ disease.
10 So, the whole goal in hepatitis B therapy is to reduce the
11 progressive necroinflammatory disease in the liver which
12 tends to be associated with persistent high levels of virus
13 replication documented usually by either persistent e
14 antigenemia or high levels of DNA or both.

15 Two slides on the key preclinical facets of
16 lamivudine. As most people here are aware, it's a potent
17 inhibitor of both HIV and hepatitis B virus in vitro at
18 nanomolar concentrations really for both viruses and in
19 various in vitro systems.

20 Lamivudine is quite potent against
21 hepadnaviruses in several models. The duck system, both in
22 primary hepatocytes and in infected ducks. Quite potent in
23 HBV infected chimps where .3 milligrams per kilogram has
24 produced clearance of detectable virus at conventional
25 hybridization assay levels. Somewhat potent in woodchucks,

1 partially potent in woodchucks as well.

2 The lamivudine triphosphate acts as an obligate
3 chain terminator for viral DNA synthesis and is not stably
4 or internally incorporated into cellular or mitochondrial
5 DNA.

6 Importantly the lamivudine triphosphate
7 molecule has a long intracellular half-life, on the order
8 of 17 to 19 hours, which facilitates once daily dosing.

9 Most of the toxicologic data was submitted with
10 the original lamivudine NDA application for combination
11 therapy in HIV briefly reviewed here. Preclinical tox
12 studies predicted an overall favorable safety profile. We
13 saw no effects in in vivo mutagenicity and carcinogenicity
14 studies, including long-term carcinogenicity studies. In
15 teratogenicity and reproductive studies, there were no
16 findings except for an increased early fetal resorption
17 rate in rabbits. PK studies in animals essentially
18 predicted good oral absorption and a large volume of
19 distribution.

20 We've conducted an extensive clinical program
21 in both HIV and hepatitis B patients, including adults and
22 children. Of most relevance today are some dose-ranging
23 studies that we conducted in the patients with chronic
24 hepatitis B in phase II, seven principal phase II dose-
25 ranging studies where we explored doses of 5 to 600

1 milligrams per day for treatment periods of 1 to 6 months
2 with follow-up added on to that as well. You'll see a
3 little bit of that data in the Q&A.

4 These are the principal PK results with
5 lamivudine in both hepatitis B and HIV patients. The drug
6 is well absorbed. The time to max concentrations is always
7 under 1 and a half hours. Cmax on the order of 1.1 to 1.5
8 micrograms per ml, and oral bioavailability around 80 to 85
9 percent.

10 There was no food effect on absorption of the
11 drug.

12 Minimal protein binding. High volume of
13 distribution in people as predicted from the animal
14 studies.

15 The clinically relevant serum half-life is 5 to
16 7 hours. The drug is primarily renally cleared as
17 unchanged drug, and therefore no dose modification is
18 needed for patients with hepatic dysfunction. But we do
19 recommend a dose modification with renal insufficiency, and
20 we can go into that detail.

21 There were no significant differences in the
22 pharmacokinetic behavior of the drug in hepatitis B or HIV
23 patients, nor by gender or ethnic group.

24 This is the principal observation in phase II
25 with regard to the dose and drug concentration relatedness

1 of the antiviral effect of lamivudine in hepatitis B
2 patients. On the vertical axis are reductions in HBV DNA,
3 serum HBV DNA, 0 to 100 percent. And on the horizontal
4 axis are the measured drug AUCs from two 1-month dosing
5 studies that were conducted in North America and Europe.

6 This recounts the doses that were explored, 5
7 to 600 milligrams per day. So, for doses of 5 to 20
8 milligrams, illustrated by these data points over here, the
9 antiviral effect was suboptimal, but at dosing levels of
10 100 milligrams and above, illustrated here by these data
11 points -- and the 100 milligram dose I should mention
12 correlated with daily AUCs over 4,000. At this kind of
13 dosing level, the antiviral effect for lamivudine in
14 hepatitis B patients was indistinguishable both with regard
15 to the percent reduction in HBV DNA, as well as the percent
16 of patients who cleared detectable virus in the solution
17 hybridization assay. So, we call this our equimaximal
18 antiviral effect. So, there's a break point in the dose
19 effect at daily doses of 100 milligrams.

20 So, the principal phase II observations for
21 hepatitis B patients were that the maximum antiviral effect
22 correlates with doses of 100 milligrams per day or greater.
23 This kind of observation from the early studies was borne
24 out in some later phase II studies and also in one phase
25 III study, the Asian multi-center trial which you'll see.

1 The 100 milligram dose proved to be superior for sustained
2 HBV DNA suppression compared to the 25 milligram dose that
3 was investigated in that phase III trial.

4 Throughout these investigations we found no
5 treatment-limiting or dose-related adverse events in these
6 kinds of dosing studies.

7 As Dr. Rubin mentioned, principally today my
8 goal will be to review the data from the four large
9 controlled phase III studies. Three of these studies were
10 conducted in treatment-naive patients, one in interferon
11 nonresponders with the thought that this group could be
12 biologically distinct. Three of these studies were
13 placebo-controlled and that included a U.S. multi-center
14 trial, as well as an Asian multi-center trial, in
15 treatment-naive patients. The study in interferon
16 nonresponders was an international study that was also
17 placebo-controlled. We conducted one what we called active
18 control design which compared lamivudine to interferon
19 monotherapy to the combination, and conducted that in
20 treatment-naive patients in Europe, Canada, and a number of
21 countries around the world.

22 This first slide illustrates the study designs
23 for the two placebo-controlled studies in treatment-naive
24 patients. This was the study that was published in the New
25 England Journal in July, a multi-center study in Southeast

1 Asia, 358 patients overall, randomized 2 to 2 to 1 to
2 lamivudine 25 milligrams per day or 100 milligrams per day
3 or placebo.

4 The commonalities of phase III included a
5 primary treatment period of 52 weeks or 1 year, if you
6 will. Those are illustrated on this slide and the next.
7 So, patients were treated for 1 year and the primary
8 treatment comparisons were at week 52 for histology as well
9 as for serologic endpoints. In this study there was no
10 follow-on period per se. Patients were offered enrollment
11 directly into a follow-on study called 3018 which you see a
12 little bit of data from.

13 The primary goal of this trial was to measure
14 improvements in liver histology. Liver biopsies were done
15 pretreatment at baseline and at 1 year.

16 This study actually was about 90 percent
17 treatment-naive. There were 10 percent of patients that
18 had some previous exposure to interferon. The other trials
19 were, in a sense, 100 percent treatment-naive.

20 The U.S. multi-center trial has been reported
21 at a meeting this spring. This study was also a 1-year
22 comparison, a straight ahead 1-to-1 randomization of
23 lamivudine 100 milligrams per day compared to placebo.
24 Treatment comparisons at week 52. A controlled off-
25 treatment follow-up period to provide controlled safety

1 assessments post treatment, 16 weeks long, and then the
2 study participation ends at week 68. 141 patients on that
3 U.S. trial.

4 This is what I mentioned as the active control
5 design study, lamivudine monotherapy for a year, 100
6 milligrams per day. This is the interferon monotherapy
7 arm, and I should mention that in this trial all patients
8 were blinded during the first 8 weeks of treatment. At
9 week 8, the investigators opened an envelope to determine
10 whether the patient was assigned to an interferon
11 treatment. There is no true placebo for interferon, as we
12 know, so at this point these two arms remain blinded to
13 each other, but the lamivudine patients continue on
14 monotherapy. So, interferon starts here on this kind of
15 design.

16 This design of this kind of treatment regimen
17 is essentially identical to the design that was used in the
18 U.S. multi-center registration trial for interferon. A
19 standard course of interferon was given here for the
20 standard 16-week regimen. Then just as in the U.S. multi-
21 center trial, primary treatment comparisons were 6 months
22 post-treatment for both histologic change and for serologic
23 markers. So, this is the nature of the data, the
24 registration studies for interferon. So, again, that fit
25 nicely with treatment comparisons at 1 year.

1 This is the exploratory combination arm in this
2 kind of study. Patients in this arm would have been taking
3 active lamivudine during the first 8 weeks as well as
4 during the interferon period, and again follow-up with
5 primary assessments at week 52.

6 The goal of this kind of design, this kind of
7 combination arm, was to explore whether pre-reduction in
8 viral load would offer an enhanced seroconverting effect
9 afforded by interferon and lamivudine during this period.

10 The interferon nonresponder trial, lamivudine
11 100 milligrams for 1 year, placebo-controlled for 1 year,
12 and then the same kind of exploratory combination arm with
13 primary treatment assessments at week 52.

14 This study had a unique feature that the
15 lamivudine patients who were half the patients overall, a 2
16 to 1 to 1 randomization. Lamivudine patients were
17 secondarily randomized 1 to 1 at this point to either
18 continue with active lamivudine or silently switch to
19 placebo. This was a way to get some control data,
20 exploratory data, for treatment beyond week 52.

21 The patient population is pretty standard for
22 those who work in the hep B arena, chronic hepatitis B,
23 surface antigenemia, e positive or DNA positive by
24 conventional hybridization, persistently elevated ALTs or
25 evidence of chronic inflammation on baseline liver biopsy,

1 and no signs of hepatic decompensation. This allowed us to
2 get control data.

3 The two principal phase III efficacy endpoints.
4 Our goal was to, number one, try to look at improvements in
5 liver disease that might be afforded by therapy. Our
6 primary analysis of reduction in the necroinflammatory
7 liver disease was a 2-point or greater decrease in total
8 Knodell Histologic Activity Index. So, that was really the
9 primary analysis of reductions in liver inflammation, if
10 you will.

11 We also felt that it would be important to
12 assess changes in liver fibrosis, so we did that as well,
13 and you'll see some of that data using a so-called ranked
14 assessment technique.

15 The e loss and e conversion analyses are
16 delineated here. E loss, of course, is reduction of e
17 antigen to below detectable. In most of the interferon
18 trials, the primary endpoint was either e loss alone or e
19 loss combined with DNA loss, and again typically measured 6
20 months post treatment in those studies.

21 The e conversion. In our program, we featured
22 the analysis of what we call full seroconversion which is
23 loss of e, gain of antibody to e, and simultaneously
24 undetectable DNA in the hybridization assay. So, this was
25 the protocol featured analysis of e conversion.

1 We had another definition because we also
2 wanted to be able to refer back to historical data from the
3 1980s or so when DNA assays were not conventionally used.
4 We looked at an alternate definition of loss of detectable
5 e and gain of antibody, and we looked at sustained e
6 conversion.

7 So, those were the two most important efficacy
8 endpoints in the program.

9 We looked at other parameters as well. ALT
10 response and sustained ALT response delineated here,
11 sustained to either end of treatment or to study end. ALT
12 levels over time, just as one looks at those in the
13 individual patient in the clinic. DNA response data and
14 DNA levels over time. S antigen loss, of course, in a
15 sense an ultimate marker of loss of infection, and then
16 safety comparisons, both clinical adverse events and
17 laboratory abnormalities.

18 Right into the baseline demographic data, quite
19 typical of adult chronic hepatitis B populations around the
20 world, patients typically ranged from their mid-20s into
21 their 50s. Mean age is illustrated here in the mid-30s.

22 The gender prevalence of the disease in the
23 population tends to be on the order of 70 to 80 percent
24 male and 20 to 30 percent female. In fact, that's the
25 ratio that we enrolled in our trial program. There is an

1 interesting biologic observation in the literature that
2 chronically infected females from childhood appear to have
3 a higher rate of spontaneous resolution of this disease,
4 and the disease in females may be milder in adults.

5 The two most prevalent ethnic groups in our
6 studies were caucasians and Asians, as illustrated here,
7 but other groups were included as well in the worldwide
8 program.

9 In each trial in the case record form, we asked
10 for recognized possible routes of acquisition of this
11 infection typically recounted by the patient to the
12 physician. The three most important categories -- overall
13 the most important category was unknown. Most patients
14 didn't seem to know how they got their HBV infection, and
15 that may actually reflect worldwide reality. Now, in the
16 West, the second most common category was history of sexual
17 contact with a known infected individual. This was a
18 relatively uncommonly recognized route of acquisition in
19 the multi-center Asian study. In the Asian study, the most
20 common category, other than unknown, was known vertical or
21 perinatal acquisition, if you will, whereas this category
22 finished in third place in the three western studies.

23 The baseline disease characteristics, again
24 quite typical of an adult chronic hepatitis B population
25 and similar in many respects to the interferon trials.

1 Baseline histologic activity index on the order of 7 to 10
2 in most of the studies except for the European/Canadian
3 active control study where the baseline score was somewhat
4 lower, possibly due to pathologist variation.

5 The percent of patients with cirrhosis in the
6 treatment-naive studies was pretty typical, 5 to 10
7 percent. The interferon nonresponders did have a higher
8 proportion of patients who had histologic cirrhosis at
9 baseline.

10 DNA levels across phase III averaged around 100
11 picograms, quite similar to the interferon studies.

12 In the three western studies, baseline ALT
13 levels were typically around 2 and a half to 3 times the
14 upper limit of normal, as had also been previously observed
15 in interferon studies.

16 In the Asian multi-center trial, this is the
17 only study where we allowed patients with normal ALTs to
18 come on study by protocol, and they comprised about a third
19 of the patient population overall. So, the median ALT in
20 that study was lower.

21 So, right into the results, if we could. These
22 are the results of the treatment comparisons on the primary
23 endpoint of a 2-point or greater decrease in Knodell HAI,
24 which we defined as histologic response. In the three
25 placebo-controlled studies, the Asian multi-center study,

1 the U.S. multi-center study, and the international
2 interferon nonresponder study, in all three, this was the
3 primary treatment endpoint. We see a very consistent
4 treatment effect with regard to lamivudine patients
5 achieving a histologic response significantly more often
6 than placebo treated patients in yellow here. This
7 compares and was always highly statistically significant.

8 Here's the overall phase III result for
9 histologic response, now including the European/Canadian
10 study of interferon nonresponders and including the
11 combination therapy arm from -- I'm sorry -- the
12 European/Canadian study in treatment-naive patients and the
13 international study with interferon nonresponders had a
14 combination therapy arm.

15 You've seen this data on the previous slide.
16 Here's the lamivudine versus placebo comparisons from the
17 three placebo-controlled studies. This now includes the
18 histologic comparisons to interferon monotherapy as well as
19 combination.

20 One important message from our program is that
21 in these kinds of combination designs, at least, we did not
22 really see any real advantage for that kind of combination
23 therapy regimen histologically or serologically, as you'll
24 see.

25 Interferon monotherapy. The overall result for

1 treatment arms containing interferon tended to be in the .
2 overall program intermediate between lamivudine and placebo
3 but within the European/Canadian study, lamivudine had a
4 slightly higher percent but was not distinguishable from
5 interferon in that particular analysis. The overall lowest
6 response rates were in the combination arm.

7 Now, this is the analysis of the other
8 important histologic endpoint that I mentioned earlier, the
9 worsening of fibrosis over the course of a year of study.
10 We felt this was important insofar as it may be a link to
11 long-term benefit. It may connect with an ability to
12 retard the progression to cirrhosis. We also felt it might
13 be difficult to show improvements in scarring of the liver,
14 but at least an effective antiviral might be able to retard
15 progression of hepatic fibrosis.

16 Here we see the result of the two treatment-
17 naive studies in which the lamivudine treated patients,
18 again in red, experienced a progression of fibrosis
19 significantly less often compared to the placebo patients
20 in yellow. Both of these comparisons were highly
21 significant.

22 In the interferon nonresponder study, we did
23 not achieve significance for this kind of treatment
24 difference which was in the same direction, but overall
25 patients had a lower progression in their fibrosis possibly

1 | because they already had advanced disease at the time at
2 | baseline.

3 | Some of the principal serological endpoints are
4 | illustrated in the next few slides. HBe antigen loss
5 | generally precedes or is sometimes simultaneous with the
6 | detectability of antibody to e, but we display the e loss
7 | results first because often biologically this is the first
8 | thing that's observed in the clinic. This was also the
9 | principal endpoint used in most of the interferon studies
10 | earlier in this decade.

11 | So, in the western trials, we consistently saw
12 | e antigen loss rates at 1 year above 30 percent. Somewhat
13 | ironically, for a reason you'll see in a moment, the
14 | highest e antigen loss rate was actually in the interferon
15 | nonresponders, 33 percent in the lamivudine group versus 13
16 | percent in placebo in that study. These comparisons were
17 | not statistically compared because, as I mentioned, we
18 | featured the analysis of what we called full seroconversion
19 | for statistical analyses.

20 | Importantly in the European/Canadian study, the
21 | e antigen loss rate at 1 year for lamivudine in red and
22 | interferon in teal was identical, 22 percent in both
23 | treatment groups. There was a somewhat higher rate in the
24 | combination arm, but as you'll see on the next slide,
25 | seroconversion, while being somewhat higher on the

1 combination arm in that European/Canadian study, was not
2 actually statistically significant in the primary intent-
3 to-treat analysis. So, for full seroconversion, what we
4 saw again was that full seroconversion in treatment-naive
5 patients, both in the Asian study and the U.S. study, was
6 significantly better on lamivudine.

7 For the interferon nonresponder study, we had a
8 paradox. I showed you the 33 percent e loss rate at a
9 year, 13 percent in placebo. It appears that perhaps in
10 interferon nonresponders, the development of the antibody
11 to e is somewhat delayed for reasons that are unknown at
12 this point. Full seroconversion and e loss were the same
13 in the placebo group in this study, 13 percent, whereas in
14 the lamivudine arm, 33 percent of patients lost e at a year
15 and only 18 percent had gained had gained anti-e to fill
16 this kind of response definition. The lowest rate of
17 serologic response was in fact in the combination arm.
18 Again, the seroconversion rate for lamivudine monotherapy
19 and interferon was statistically indistinguishable at 1
20 year.

21 Here's kind of a clinician-friendly slide.
22 This is ALT levels over time in the patient cohort in the
23 three placebo-controlled studies, placebo in yellow,
24 lamivudine in red. As we saw in the last phase II study,
25 patients treated with lamivudine for 6 months or more

1 tended to normalize their ALTs, and so the dotted line here
2 indicates the upper limit of normal of ALT.

3 Incorporating our ALT response definitions,
4 probably the most important one was sustained ALT
5 normalization in which patients had to achieve two normal
6 ALTs and had to maintain that response to the end of the
7 primary treatment period. That kind of observation
8 occurred in 40 to 72 percent of lamivudine treated patients
9 versus 7 to 24 percent of placebo. Those comparisons were
10 always highly significant.

11 The comparison of sustained ALT normalization
12 for lamivudine compared to interferon in that
13 European/Canadian multi-center study was in fact
14 statistically significant favoring lamivudine monotherapy.
15 So, lamivudine produced sustained ALT normalization in that
16 study in 40 percent of patients compared to 17 percent of
17 the interferon monotherapy patients.

18 We think that these kinds of effects on
19 traditional, if you will, clinical laboratory markers of
20 disease are due to the kind of marked antiviral effect that
21 we saw in phase II and this simply illustrates the phase
22 III antiviral effect for lamivudine in the three placebo-
23 controlled studies. For lamivudine treated patients, their
24 first visit in the phase III protocols is week 2, and you
25 can see marked drops by week 2.

1 I need to point out that for the purposes of
2 this kind of display, we actually arbitrarily assigned a
3 value of .8 picograms to undetectable DNA values. We have
4 two types of PCR related data that suggest that the average
5 antiviral effect of lamivudine is actually more like 3 to 4
6 logs. So, this kind of display is somewhat artifactual in
7 that negative, undetectable values were assigned a value of
8 .8, half the threshold of detectability, so obviously a
9 very marked difference in DNA reductions in placebo versus
10 lamivudine over the course of a year.

11 So, the summary of our efficacy observations is
12 we saw consistent reductions in hepatic necroinflammatory
13 activity in both Asian and western patients, significant
14 reduction in the progression of fibrosis in the treatment-
15 naive patients, enhancement in e loss and e conversion in
16 treatment-naive patients. We saw e loss and e
17 seroconversion rates at 1 year that are similar to
18 interferon, essentially identical to interferon. There is
19 some confusion in the literature there because again the
20 interferon studies tended to analyze e loss and we've
21 tended to feature the full e conversion definition. And as
22 you saw, we saw significant enhancement of ALT
23 normalization.

24 Into the safety observations. First we'll see
25 the comparisons of lamivudine to placebo and then

1 lamivudine to interferon. These are the composite
2 observations for clinical adverse events, lamivudine versus
3 placebo, events in decreasing order of frequency as
4 observed in the trials. As you see, line by line as one
5 goes down to compare lamivudine versus placebo, there
6 really aren't any appreciable distinctions for clinical
7 adverse events between lamivudine and placebo in chronic
8 hepatitis B patients over a year.

9 This just continues that list at lower
10 frequency levels down to the 5 percent event level, but the
11 observations continued down throughout.

12 The comparison for lamivudine to interferon is
13 primarily available as a direct head-to-head comparison
14 within the European/Canadian study, the so-called B3010
15 study. Here again are the clinical adverse events in
16 decreasing order of frequency.

17 Now, the clinical adverse events were, as you
18 might expect, overall more common on the interferon arm. I
19 want to highlight just a few here for clinical
20 consideration.

21 Some of these events such as fever and chills,
22 malaise and fatigue, headache, myalgias are known
23 components of the flu-like effects of interferon and most
24 patients can be treated through those kinds of effects.
25 The GI side effects are occasionally included in the flu-

1 like effects of interferon by some authors.

2 However, there are other kinds of adverse
3 effects that one sees with interferon that aren't
4 necessarily part of the flu-like syndrome and tend to be a
5 little more persistent and problematic in patients: hair
6 loss and alopecia. There were some CNS effects that we
7 observed in these patients. Dizziness, depressive
8 disorders, and then as you'll see on the next slide,
9 vertigo were all more common in the interferon treated
10 patients. Some other aspects of interferon. Again these
11 are generally well described in interferon labels.
12 Leukopenia, if you will, was significantly more common in
13 interferon versus placebo patients. Anorexia and weight
14 loss were more common with interferon. Joint aches and
15 pains more common and thrombocytopenia as well. So,
16 clinical adverse events -- it appeared that interferon was
17 less well tolerated.

18 Interestingly enough, in the composite data of
19 clinical laboratory abnormalities during the primary
20 treatment periods, the rate of grade 3/4 ALT elevations was
21 identical in lamivudine treated patients and placebo
22 treated patients illustrated here. There was also no
23 appreciable difference in the occurrence of amylase and
24 lipase elevations relating to the old issue of
25 pancreatitis, if you will. So, the two drugs looked quite

1 similar. There may be a somewhat higher frequency of CPK
2 elevations, but as we can see on a slide, that didn't seem
3 to have any real substantial impact clinically.

4 We did special analyses of the issue of post-
5 treatment ALT elevations because these have been observed
6 with vidarabine in the 1980s. They have also been observed
7 with interferon. So, we incorporated kind of a four-tiered
8 analysis of during-treatment and post-treatment ALT
9 elevations. The mildest form of elevation will be just a
10 twofold times baseline for an individual patient. Three
11 times baseline, a little more common, and this tends to
12 correspond to a so-called grade 3 abnormality.

13 Then the more clinically interesting one tends
14 to be when the patient gets to ALT levels over 500, at
15 which time one might schedule an extra clinical visit or
16 start to get a little concerned. Especially important, of
17 course, are ALT elevations associated with signs of hepatic
18 insufficiency such as bilirubin elevations or clinically
19 serious adverse events.

20 What we observed when we combined the data from
21 those controlled follow-up periods, I should say what we
22 observed during treatment was no difference between
23 lamivudine and placebo for these kinds of phenomena. But
24 post-treatment we did see a difference and that's
25 illustrated here, a mild overall difference between

1 lamivudine and placebo for the total event observation
2 rate. The difference tended to be in the kind of mild to
3 moderate, generally asymptomatic for post-treatment ALT
4 elevations, roughly twofold more common with lamivudine
5 compared to placebo, a little more than twofold.

6 But importantly, there was no difference in
7 clinically severe events post-treatment between patients
8 coming off lamivudine and patients coming off placebo.
9 Those were analyzed in two ways. One was ALT elevations
10 associated with bilirubin elevations, in which case 2
11 percent of placebo patients and 1 percent of lamivudine
12 patients exhibited this kind of phenomenon in the post-
13 treatment period. No difference there.

14 And also for clinical serious adverse events, 2
15 of 200 placebo patients and 5 of 416 lamivudine patients,
16 about a 1 percent post-treatment event rate there for
17 clinically severe adverse events.

18 Importantly, in the phase III studies, no
19 patients developed clinical liver failure.

20 With regard to the overall summary of SAEs,
21 deaths, and withdrawals, serious adverse events about the
22 same rate in lamivudine and placebo, 10 and 11 percent
23 respectively. The most common abnormality reported as an
24 SAE was abnormal liver function tests, generally elevated
25 ALTs.

1 There were no deaths in the primary phase III
2 controlled studies. We did see some deaths in transplant
3 patients in some of the other studies which can be
4 discussed otherwise. Those were generally of the types
5 expected in those patient populations.

6 Withdrawals were actually a little more common
7 in placebo patients than lamivudine patients in the phase
8 III program, I think emphasizing the underlying severity of
9 the disease. This proportion of patients, 2 and 3 percent
10 respectively, withdrew for adverse events. Other
11 withdrawals were for miscellaneous reasons.

12 So, the summary of the safety observations
13 essentially is that the clinical adverse events and
14 laboratory abnormalities were similar to placebo during
15 treatment. There was a modest increase in generally
16 asymptomatic post-treatment ALT elevations, but no increase
17 in clinically severe events.

18 Now, the important issue of antiviral
19 resistance, which of course is relevant to any
20 antimicrobial. With lamivudine, we in a sense had an
21 advantage on this issue because we knew prior to the
22 development program that the YMDD motif, a four amino acid
23 sequence, is conserved between the HIV reverse
24 transcriptase and the hepatitis B reverse transcriptase,
25 and it was known in HIV that this might be a site of

1 resistance essentially to mutation. So, we prospectively
2 incorporated into the phase III program some comprehensive
3 analyses of the phenomenology of detectable YMDD variants.

4 The way we did that was to take all available
5 patients at week 52 and at week 104, at the end of 1 and 2
6 years of study. For patients who had detectable YMDD
7 variants, we then tracked back on their previous sera to
8 determine when the YMDD variant developed. We used PCR
9 methods to amplify DNA and then do a restriction fragment
10 length polymorphism assay to detect the variants.

11 The overall result of this was that YMDD-
12 variant HBV were detectable at 1 year in the overall
13 studies in 16 to 32 percent of patients at 1 year; 24
14 percent overall phase III average.

15 Now, in the limited year 2 data we have, the
16 multi-center Asian cohort has been carried to 2 years now.
17 We saw a 38 percent incidence of detectable YMDD variants
18 in those patients after 2 years compared to 16 percent in
19 the 1-year study group.

20 Importantly, however, the clinical
21 phenomenology associated with this -- it appears that there
22 is not necessarily a complete loss of clinical response.
23 what we see in patients is that patients with the YMDD
24 variants tend to maintain lower viremia levels, lower HBV
25 DNA and ALT levels compared to their pretreatment values.

1 They were also significantly better than
2 placebo in several comparisons. The sustained HBV DNA
3 response, for example, was not as good as the patients who
4 retained wild-type, but it was significantly better than
5 placebo after adjustment for baseline covariates.

6 We saw significantly improved liver histology
7 in the patients with the variants, compared to placebo
8 patients at 1 year, and improved ALT normalization.

9 So, they retained many of the elements of
10 clinical response.

11 The one thing that appeared to be perhaps lost
12 was e conversion did not appear in the overall analysis to
13 be significantly greater than placebo. However, patients
14 with the variants do seroconvert, and we're still looking
15 at that issue. Interestingly enough, in the Asian cohort
16 at 2 years with the longest carried-forth cohort, the
17 seroconversion rate in the patients with the variants is 27
18 percent cumulatively after 2 years.

19 There were no safety issues identified with the
20 variants. Patients who developed the variants had a low
21 higher incidence of on-treatment ALT elevations but lower
22 incidence at post-treatment, and overall the safety
23 comparisons were not different for any adverse events.

24 This is important data in the program on the
25 next two slides. This is the Asian multi-center trial.

1 The first year of treatment is the 3009 study published in
2 the New England Journal to this point. This is the same
3 patient cohort. 90 percent of the patients were carried
4 into a follow-on study called 3018.

5 This shows the lamivudine treated patients over
6 2 years divided into two kinds of patients, patients who
7 kept the wild-type illustrated by the solid dotted lines
8 for ALT levels and DNA, and that was the majority of
9 patients. Patients who developed the variants are
10 illustrated by the hatched lines for ALT and DNA.

11 With regard to virologic response over 2 years,
12 both groups obviously did well in the first year. Patients
13 start to develop the variants in the second half of the
14 first year. After 2 years, the subgroup with the variants
15 was still finishing 80 to 90 percent reduced in their DNA
16 levels compared to their own pretreatment.

17 This is the corresponding ALT phenomenology.
18 Patients who developed the variants tend to have higher ALT
19 levels pretreatment compared to those who retain wild-type,
20 but as you see here, even the total cohort with the
21 variants at 2 years, the median ALT was 0.9 times the upper
22 limit of normal, in other words, within the normal range.
23 This was 0.7 times normal. So, both finished with normal
24 ALTs at 2 years for the overall cohort.

25 This is possibly an even more important

1 analysis. With that kind of previous analysis, that
2 includes patients who develop variants in the second year.
3 Here we've taken the same database but analyzed the data,
4 limited the analyses to patients who develop the variants
5 in the first year, so that we could then follow that kind
6 of cohort forward for another year, so we'd get a full year
7 of additional observation on a cohort who had the YMDD
8 variants. So, again, this is the first year data, very
9 similar to what you saw before.

10 This patient population is patients who had
11 detectable YMDD variants at week 52 and week 104. What you
12 see for viral load is again patients developing the
13 variants in the second half of the first year.

14 This is the subgroup who developed the variants
15 by week 52. We see their viral load levels go up a bit.
16 They don't get back to their baseline level, and then it
17 seems to actually level off or even start to trend downward
18 during the second year just by continuing lamivudine
19 treatment.

20 The patients who maintained wild-type are
21 illustrated here, and again these patients, with
22 undetectable levels, are all assigned a .8 picogram value.

23 So, there was this kind of what we often call
24 the blip phenomenon with regard to viremia. The viral load
25 often comes up a bit but then seems to stabilize, and in

1 many patients it actually goes down. We can see this in
2 individual patients.

3 The associated ALT phenomenology is, of course,
4 in patients with wild-type, again they tended to have lower
5 ALT levels pretreatment. They come down and normalize
6 nicely.

7 Patients who developed the variants in the
8 first are illustrated here. They come down initially with
9 good ALT response. As they develop the variant subspecies,
10 they start to get an ALT elevation, but again echoing the
11 viremia, the ALT levels seem to stabilize and drop off in
12 year 2.

13 There are some important preclinical evidence
14 that these YMDD variants may be less replication competent,
15 and some of that has been published now. The variants
16 appear to replicate to lower levels in tissue culture,
17 reported by several different laboratories. Also, work on
18 the variant polymerases, when the methionine is changed to
19 either valine or isoleucine, the methionine at position
20 552, these are the two mutation patterns we see.

21 People have worked with those polymerases
22 either cloned or extracted from variants, and it appears
23 that these polymerases not only have reduced affinities for
24 lamivudine triphosphate but also for natural nucleotide
25 substrates. That may explain why the replication overall

1 is lower with the variants.

2 The clinical evidence for less replication is
3 what I just showed you to some extent. Patients tend to
4 maintain HBV viremia compared to their pretreatment values
5 when they had wild-type. We have a couple of dozen
6 patients overall who have been discontinued when they
7 developed YMDD variants. What we find there is
8 consistently the virus that returns and becomes the
9 predominant species over time is the wild-type,
10 illustrating that in the absence of the selective
11 lamivudine treatment, the wild-type seems to have a
12 replication advantage.

13 We think we understand this. This is a
14 molecular model. Again, this should be considered
15 speculative, but this is a molecular model of the HBV
16 polymerase. This is the nucleotide binding pocket within
17 the HBV polymerase. This is where nucleotide triphosphates
18 bind for the enzyme function.

19 The important mutations are at the 552
20 methionine locus, and for the methionine to valine, we
21 often see the upstream isoleucine -- leucine to methionine
22 switch. Well, these two points are very close to the
23 nucleotide binding pocket, and we think what may be
24 happening is that the shape of this binding pocket in the
25 enzyme actually changes a little bit, resulting in

1 decreased affinities for lamivudine triphosphate and other
2 nucleotide triphosphates.

3 So, the phase III data regarding YMDD variants
4 -- we mentioned the overall incidence. We showed you the
5 data that patients with variants tend to maintain lower
6 viremia and retain at least partial virologic response
7 overall, typically 80 to 90 percent reduced at 1 or 2 years
8 compared to their own pretreatment levels. And patients
9 with the variants retained significant elements of clinical
10 response as we showed. And the in vitro data for reduced
11 replication competence.

12 Briefly reviewing the other studies, we have
13 four open-label treatment transplant studies. It's very
14 difficult to do placebo-controlled studies in patients with
15 life-threatening disease.

16 In these studies, we thought we saw promising
17 antiviral effects, reductions in HBV DNA, as you might
18 expect, and in patients with elevated ALT levels at
19 baseline, there appeared to be an ALT normalizing effect.
20 Bilirubin levels improved in the subgroups but had
21 hyperbilirubinemia pretreatment, and albumin levels
22 appeared to improve in some groups as well.

23 Importantly, we did see more adverse events and
24 serious adverse events in these patient populations. It
25 appeared they were generally of types expected with liver

1 failure, surgical complications or immunosuppression. We
2 didn't see any new pattern of adverse events that we could
3 pick out.

4 Some important follow-on studies are currently
5 ongoing. One is actually wrapped, a phase IIb study where
6 explored treatment past a year in an open label fashion.
7 With treatment up to a year and a half, we saw e antigen
8 loss in 10 or 24 patients, 42 percent.

9 The current phase IIIb, if you will, or III
10 follow-on studies include some follow-on treatment studies
11 for Asian patient cohort and for the North
12 American/European patient cohorts. These are open-label
13 treatment with lamivudine for up to 5 years.

14 The interim analyses submitted with the NDA
15 indicated we do appear to be seeing some increment in e
16 loss and seroconversion in year 2 for both Asian and
17 western patients.

18 There's an observational follow-on study for
19 patients who achieved e conversion during phase III. The
20 question is how durable is that when patients are taken off
21 treatment. That's called our 3016 study, and the results
22 of that look quite promising. Patients are coming on to
23 this study with an average of 4 to 6 months median follow-
24 up, 6 months for the lamivudine treated ones. The e has
25 remained negative post-treatment for a median of 6 months

1 in 94 percent of patients.

2 We haven't really seen any different safety
3 observations with these longer-term follow-on studies.

4 We did a pediatric dosing study in Europe and
5 Canada. 53 children and adolescents received one of five
6 doses. We did see rapid DNA reductions in these patients
7 as we expected. These were children with chronic hepatitis
8 B with active disease, rapid HBV DNA reductions. Here we
9 used the Chiron branched DNA assay.

10 It appeared in this study that a dose of 3
11 milligrams per kilogram per day produced similar exposures
12 to the exposures in adults at which the equimaximal
13 antiviral effect was achieved. And we saw in kids as well
14 that at that dosing level -- above that dosing level, I
15 should say, the antiviral effects appeared comparable.

16 We saw no treatment-limiting or dose-related
17 adverse events in the pediatric dose-ranging study.

18 So, I think as Dr. Rubin alluded to, we expect
19 two kinds of long-term benefit with lamivudine. There's a
20 proportion of patients who will lose e or seroconvert, if
21 you will. That proportion appears to be essentially
22 identical to what you achieve with a full course of
23 interferon therapy at 1 year. We also feel we have an
24 increment in response at 2 years. But in any case, we do
25 see that kind of patient population and the literature

1 | would suggest there is some long-term association with
2 | improved clinical outcomes with those kinds of patients.

3 | As Marc mentioned as well, we have plenty of
4 | data to show that in patients who don't happen to
5 | seroconvert, we do see histologic improvement in liver
6 | disease and improvement in ALTs and other clinical
7 | benefits.

8 | Our conclusions then are that we've got
9 | substantial clinical data derived from nearly 40 studies,
10 | to which I think Dr. Jolson might have been alluding, where
11 | we see consistent efficacy and excellent tolerability for
12 | lamivudine in Asian and western patients, reduced liver
13 | inflammation, reduced progression of fibrosis, enhanced e
14 | loss and e conversion, and ALT normalization. We think
15 | these effects are due to prolonged suppression of virus
16 | replication, including partial suppression in the patients
17 | who develop the variants.

18 | The safety profile of lamivudine appears
19 | comparable to placebo during treatment. There is a modest
20 | increase in post-treatment ALT elevations, generally in the
21 | grade 3 variety, and generally asymptomatic. No difference
22 | in clinically severe events post-treatment compared to
23 | placebo.

24 | The data support the idea that lamivudine
25 | monotherapy will in fact benefit many hepatitis B patients

1 worldwide, and we feel is a major therapeutic advance based
2 on its oral bioavailability, as well as its consistent
3 efficacy and safety. The data from that follow-on study,
4 as well as the e antigen data in the program in the study,
5 support the notion that one could consider treatment
6 discontinuation after e conversion in immunocompetent
7 patients. Patients who are immuno-debilitated or on
8 immunosuppressant drugs are known to have a significant
9 risk for reactivating disease, so we do not recommend it in
10 those kinds of patient populations.

11 I appreciate it.

12 DR. HAMMER: Thank you very much.

13 We have time for targeted questions, perhaps 30
14 minutes or so. I'm going to go around the table. I'd like
15 to ask the committee members to prioritize their questions
16 and ask perhaps their most pressing first two or three
17 questions in deference to other members of the committee
18 who likely have similar questions. I will start on the --
19 did you have something else to present?

20 DR. COCCHETTO: Sorry, Dr. Hammer. David
21 Cocchetto. Dr. Goodman was prepared to make some comments
22 on histopathology in this patient population as well.

23 DR. HAMMER: I apologize.

24 DR. BROWN: That was my confusion on the
25 agenda, but Dr. Zak Goodman from AFIP would like to briefly

1 present some of the histologic observations from the
2 program.

3 DR. GOODMAN: My name is Zachary Goodman, and I
4 am the pathologist who evaluated the liver biopsies from
5 the 3010 and 3011 studies. I was asked by the sponsor to
6 present some of the data and talk about scoring of
7 biopsies.

8 There are many ways that you can approach
9 evaluation of liver biopsies in a study such as this. I've
10 got them listed on the slide here. The old-fashioned way
11 is the conventional diagnoses of chronic persistent and
12 chronic active hepatitis. That's not adequate, but there
13 are many other ways that have been devised. I'll tell you,
14 just summarize. I've tried all of these and they all work
15 pretty much to the same degree. The one that has been used
16 the most, though, is one which is one of the older ways
17 which is the Knodell score, which is what was used for this
18 study.

19 Now, the Knodell score really should be called
20 the Knodell-Ishak score because my colleague Kamal Ishak is
21 the pathologist who devised this way of evaluating liver
22 biopsies. This was a scoring method that Drs. Knodell and
23 Ishak came up with in planning a study similar to this type
24 of treatment trial in the 1970s. The study itself was
25 never funded, but they published their method for

1 evaluating the biopsies.

2 This was designed so that they could take a
3 large number of biopsies from many patients and come up
4 with some sort of numerical score that could then be used
5 in statistical studies. It wouldn't be used in evaluating
6 a liver biopsy from an individual patient.

7 What they did was they realized that you could
8 dissect out the different components of injury that one
9 sees histologically. There's the periportal injury. The
10 old term is "piecemeal necrosis," and you could evaluate
11 the degree of that feature and then give that a numerical
12 score and add in extra points if there's severe injury with
13 bridging necrosis. You can do the same for the parenchymal
14 injury or the lobular injury, the portal inflammation, and
15 the same for the fibrosis. Each of these gets a numerical
16 score and then you add them up, and that's what gives you
17 the histologic activity index.

18 Of course, once you've gotten this data, you
19 don't really have to add them in any particular way. You
20 can evaluate each one separately. You can take out the
21 fibrosis and look at that separately and so forth. But it
22 is a way to approach a large number of biopsies in a fairly
23 uniform fashion.

24 So, what I'm going to talk about is how we go
25 about doing that and then show some examples from the

1 placebo-controlled U.S. trial. Just to refresh your
2 memories, those of you who are a ways out of medical
3 school, this is what a normal liver looks like
4 histologically under the microscope. There are portal
5 areas and each portal area has a portal vein branch, an
6 hepatic artery branch, and a branch of the bile duct. The
7 blood comes in through the small portal tracts and
8 percolates through the sinusoids of the liver, bathing the
9 hepatocytes with blood that's both from the portal venus
10 system and from the systemic circulation where the business
11 of the liver takes place. Eventually the blood reaches the
12 central veins and then exists into the systemic
13 circulation.

14 This is a high power of a normal, very small
15 portal area. This is just to show each portal area has a
16 portal vein branch, an hepatic artery branch, and a small
17 bile duct. There's a little bit of fiber supporting stroma
18 that varies with the size of the portal area. This one is
19 very small, so it doesn't have very much. You notice there
20 are no inflammatory cells here.

21 Here's a liver biopsy from one of the patients
22 in the study. When there is chronic hepatitis, there are a
23 lot of chronic inflammatory cells that accumulate in the
24 portal area. Here's the portal vascular structures pushed
25 over to the side. The entire portal area is expanded by

1 chronic inflammatory cells, lymphocytes. Now that we have
2 surface marker studies, we know that most of the
3 inflammatory cells in the center of the portal area are B
4 cells. They sit there and they do their function I suppose
5 of making immunoglobulins, and they tend to stay there
6 after a lot of the other injury dies down. That's probably
7 the least important component of the score.

8 What's more important is the injury that takes
9 place out at the periphery, at the interface between the
10 parenchyma and the portal connective tissue where T cells
11 are found. The T cells come in contact with the liver
12 cells and cause them to die. That's through a process
13 which goes by several names. The current popular name is
14 interface hepatitis, but the older name is piecemeal
15 necrosis, which was defined as the destruction of liver
16 cells at this interface between parenchyma and connective
17 tissue.

18 Here is it as high power from one of our
19 patients, and you can see the lymphocytes are coming in
20 contact here with the liver cells. They push their way
21 into the liver cells. They lay down adhesion molecules.
22 They express cytokines, and the lymphocytes -- these are T
23 cells -- send a signal to the liver cells that you are
24 irreversibly infected with the virus and now it's time to
25 undergo apoptosis, activate your suicide genes and die.

1 And that's what happens. The liver cells die and they're
2 replaced by the expanding portal area.

3 So, that's something that we can grade. If
4 it's hard to find them, you can search around and find a
5 little focus where there's interface hepatitis B, that
6 would be considered mild.

7 According to Knodell and Ishak's definition if
8 most of the portal areas have some interface hepatitis, but
9 it's less than 50 percent of the way around the majority,
10 then that would be considered moderate. So, here we have a
11 portal area where there's no interface hepatitis on this
12 side, but there is on this side. So, that would be
13 moderate.

14 And if it's more than 50 percent of the way
15 around most of the portal areas, then that's considered
16 marked.

17 Now, I can take a good size liver biopsy and
18 I'll find examples of mild, moderate, and marked in some of
19 the portal areas in each biopsy. So, you have to do a
20 mental average of the overall degree of injury to come up
21 with the score. That's one of the sources of variation in
22 scoring, but it's not too bad.

23 So, we grade them as mild, moderate, and marked
24 and then look back at the score sheet and assign a number
25 that goes along with these. Mild, according to the

1 original definition gets a score of 1. Moderate gets a
2 score of 3, and marked gets a score of 4.

3 Then we can add in extra points if there's
4 severe injury with bridging necrosis. That only happens
5 rarely in viral hepatitis. It's more frequent in
6 autoimmune hepatitis. In the original definition, if you
7 had a moderate degree of piecemeal necrosis plus bridging,
8 you get a score of 5. I've never seen an example of that.

9 You do occasionally, in viral hepatitis, see a
10 marked degree of piecemeal necrosis with portal to portal
11 bridging or portal to central bridging and that gets a
12 score of 6.

13 On very rare occasions in viral hepatitis there
14 will be such severe injury that large portions of the
15 parenchyma are destroyed, there's multilobular necrosis,
16 and that would get a score of 10. But a patient with that
17 much injury would be too sick to be in one of these
18 studies. I have very rarely seen this in chronic viral
19 hepatitis, but never in one of these studies.

20 So, for practical purposes, the numbers we get
21 are 0, 1, 3, 4, and 6. It's a discontinuous score. I
22 think that was because the authors originally tried to
23 weight it as to what they thought was the biologic
24 potential of these lesions.

25 Now, the other component of the injury is the

1 parenchymal injury, what's going on away from the portal
2 areas, and that's where liver cells undergo apoptosis
3 through some mediated immune mechanisms. Lymphocytes again
4 come in contact with the liver cell and cause it to
5 degenerate, activate its suicide genes, fragment, and
6 undergo apoptosis. After the cell is dead, then a cluster
7 of inflammatory cells is left behind and that remains there
8 for several days. So, it allows us to see how much injury
9 has occurred recently.

10 The way to score this is to look at the entire
11 section on low power, and you get a visual estimate of how
12 many cells are undergoing degeneration necrosis. There's
13 one there, one there, one there, one there, and then there
14 are clusters of inflammatory cells showing where they have
15 died. Again, you look at the overall biopsy and decide
16 whether it's mild, moderate, or marked and assign a score
17 based on that. That's for parenchymal injury and also for
18 portal inflammation, which I won't show any more on.

19 Then we do the same for fibrosis. There they
20 set up a scoring system based on how much architectural
21 distortion there was. This was more in lines of more
22 permanent forms of injury. If it's just portal or
23 periportal scarring, that gets a score of 1. If there's
24 extension of the fibrosis, fibrous scars from one vascular
25 structure to another that is bridging, you get a score of

1 3, and when there's cirrhosis, you get a score of 4.

2 Then we add them all up and come up with the
3 overall histologic activity index, which would have a
4 maximum score of 22, but I've only seen I think, in my 18
5 years doing liver pathology, one case of viral hepatitis
6 that had a score of 22. Really in practical terms the
7 maximum would be perhaps 18.

8 Let me first mention that when we're looking at
9 a large number of biopsies in the context of a study, the
10 scores can be quite variable from the pretreatment to the
11 post-treatment. One reason for this is the natural history
12 of the disease. We know that chronic viral hepatitis is an
13 episodic disease, that there are times when there's
14 exacerbation of the disease and times when it's quiescent.

15 There's sampling variability. The liver is a
16 1,500 gram organ and when we take a liver biopsy, we're
17 only looking at 10 milligrams of tissue, a tiny little part
18 of it. Depending on the size of the biopsy and how
19 representative it is, you can get variation in that regard.
20 I've seen a good size biopsy where one end of the biopsy
21 will have a score of 10 and the other end will have a score
22 of 0. If you have only half of the specimen, that will
23 affect the score.

24 There is some interpretation variability. At
25 some point in time, one has to make a decision. Is this

1 mild or is that moderate? Well, that's a difference of 2
2 points right there, and depending on what you had for
3 breakfast, that can affect the interpretation.

4 In the context of a large study, these should
5 all cancel out. Some will go up and some will go down due
6 to these random changes, and the overall effect will be 0.
7 Then any effect that's left will be the effect of our
8 experimental therapy.

9 So, let me show a few examples. All of these
10 are taken from the 3010 study, the placebo-controlled
11 trial.

12 On the left is the pretreatment biopsy and on
13 the right is the post-treatment biopsy. So, here we have a
14 pretreatment biopsy where there's some portal inflammation
15 here, a little bit. There's a little bit of interface
16 hepatitis and there's a little focus of parenchymal
17 necrosis out there. That would get us an inflammatory
18 score of 3.

19 Over here we have the post-treatment biopsy
20 from the same patient and he's got quite a bit of
21 inflammation here in the portal area. There's interface
22 hepatitis everywhere where we have the opportunity to have
23 it. So, we have a moderate degree of portal inflammation,
24 a marked degree of interface hepatitis, and also a marked
25 degree of parenchymal necrosis away from it. So, that

1 would get an inflammatory score of 11.

2 This patient happened to be on placebo, and so
3 probably that's the natural history of the disease. In his
4 pre-treatment biopsy, he was in a quiescent phase. Post-
5 treatment he was in a very active phase with a difference
6 of 8 in his inflammatory components of his score.

7 Here's a patient who happened to have been
8 getting lamivudine. Here's his pretreatment biopsy and
9 here's his post-treatment biopsy. Over here is a portal
10 area with a great deal of inflammation, interface hepatitis
11 all along the front here and spotty necrosis within the
12 parenchyma. Here's a little portal area, which you'll see
13 at higher power in the next -- the next slide will be a
14 higher power of this area compared to this area.

15 Here's that portal area with no inflammation,
16 really essentially normal parenchyma. Out away from the
17 portal area, we can see there are lots of clusters of
18 inflammatory cells and acidophilic bodies where there's
19 been necrosis and dropout of liver cells. So, here we have
20 a score of perhaps 11 pretreatment and a score of 0 post-
21 treatment.

22 Another patient who was getting lamivudine. I
23 should say parenthetically I didn't know this at the time I
24 was scoring the biopsies. I didn't know which ones went
25 with which and I didn't know what their order was. I just

1 had to do a score and then afterwards the code was broken.

2 This is pretreatment. We have portal
3 inflammation, interface hepatitis all along here. Post-
4 treatment here's the biopsy from the same patient, a
5 different portal area, of course, because that one was
6 taken out during the biopsy. Here's portal fibrosis here,
7 a little bit of inflammation, and a little bit, at one
8 focus, of piecemeal necrosis there. Quite a bit of
9 improvement.

10 Another patient, pretreatment over here with
11 spotty necrosis and inflammation. Post-treatment over here
12 he has essentially normal parenchyma. Now, we'll back away
13 a little bit, same biopsy. We are looking at this area and
14 this area.

15 Here are two portal areas from that patient.
16 This one is quite expanded with a little bit of
17 inflammation but a lot of interface hepatitis all around
18 it. The same thing over here. Here's a portal area here
19 which looks essentially normal, quite a difference in the
20 inflammatory activity.

21 Now, we're going to move on to fibrosis because
22 that's something else that was scored, and after scoring
23 it, then I went back and looked at these in pairs to do the
24 ranked assessment. So, notice this portal area here, and
25 this one will be in the same place on the next slide and

1 | this one will move down a little bit so we can bring
2 | another one into view.

3 | So, that's the same biopsy. The blue stain
4 | represents collagen. This portal area is expanded, so is
5 | this one. Over here we have that portal area that has
6 | virtually no fibrosis. This one up here, it was on the
7 | edge of the section, but it has just a little bit of
8 | fibrosis. So, in the Knodell score, these would each get a
9 | score of 1, but you can see there's a difference between
10 | the pretreatment and the post-treatment. Dr. Brown talked
11 | about worsening of fibrosis, but actually in this case the
12 | fibrosis got better.

13 | And I'll show a couple more examples. Here's
14 | another one. These are all where the fibrosis got better.
15 | Pretreatment there's bridging fibrosis here. Post-
16 | treatment it's a little bit dark but a couple of portal
17 | areas with just a little bit of portal fibrosis. Now, some
18 | of this could be sampling, of course, but overall there
19 | were many more that improved in the lamivudine treated
20 | group than in the placebo treated group, and on the other
21 | hand, in the placebo treated group more of them went the
22 | other way.

23 | And one last slide showing quite a bit of
24 | bridging fibrosis here in the pretreatment and still some
25 | bridging fibrosis but much less in the post-treatment.

1 So, some of this of course could be sampling
2 variability. I don't think it's all interpretation
3 variability. Some of it could be the natural history of
4 the disease, but when you look at the overall cohort,
5 there's obviously an effective therapy.

6 So, now I'll turn it back over to Dr. Brown for
7 questions.

8 DR. HAMMER: Nothing more formal. Okay, thank
9 you.

10 I'll just rewind the tape to my previous
11 comments. We're going to go around the table to ask some
12 questions. We have limited time today and we'll have more
13 time for questions this afternoon. So, I'd ask you to
14 prioritize your questions and just ask your top one, two,
15 or three questions in deference to your colleagues. I'll
16 start on my left with Dr. Fletcher. Do you have any
17 questions for the sponsor?

18 DR. FLETCHER: Thank you. My question concerns
19 for patients that may take lamivudine for hepatitis B how
20 truly confident we are that 100 milligrams a day is the
21 optimal dose. The pharmacodynamic modeling indicating the
22 plateau effect, while compelling, is done from short-term
23 studies at approximately 1 month, but the peak clinical
24 effect doesn't seem to occur until at least 6 months or so
25 of therapy. So, given the safety profile of the drug, how

1 do we know that a larger dose would not produce a response
2 in a greater number of patients for a more prolonged period
3 of time?

4 DR. BROWN: We should have a slide shortly on
5 that issue, M-87.

6 These are the principal findings we've had in
7 the program with regard to the dosing effects of lamivudine
8 in hepatitis B patients. I mentioned the phase II dose-
9 ranging effects, but I think as was just mentioned, those
10 were relatively short-term treatment periods.

11 The phase III study, the Asian multi-center
12 study which included the 100 milligram 1-year treatment
13 cohort as well as the 25 milligram treatment cohort, showed
14 a superiority for the 100 milligram cohort over the 25 for
15 sustained HBV DNA suppression.

16 I should mention we have some PCR data from two
17 different studies. I may have mentioned it briefly. They
18 would indicate, just as we saw no difference for doses
19 above 100 milligrams per day, we saw no difference for HBV
20 DNA reduction or clearance, if you will, in the standard
21 assay. When we looked at PCR data both in adults and
22 children, we found no difference in proportion of patients
23 who clear by PCR for doses above 100 milligrams. Those
24 explored doses to about 300 milligrams essentially.

25 So, we have some limited PCR data to support

1 the notion that we have the dose at which one achieves a
2 maximal antiviral effect. Doses above that really would be
3 difficult to distinguish an antiviral effect without
4 infinite sample size essentially because of the existing
5 data suggesting no appreciable difference within the
6 program.

7 Of course, one of the key things that dose may
8 play into is the whole issue of the incidence of the
9 variants with reduced susceptibility. That's kind of a
10 traditional issue in antiviral therapy.

11 Importantly in this program, we saw no
12 difference in the incidence of YMDD variants in the large
13 multi-center Asian study. We saw no difference in the
14 incidence of YMDD variants in the 25 milligram or 100
15 milligram cohort, even though this cohort had a superior
16 antiviral effect. The incidence of variants was
17 indistinguishable in these two cohorts at a year, and as
18 well we did a fair amount of regression modeling to look at
19 the issue and we didn't see any dose effect there either.
20 So, although it might be reasonably expected that there
21 could be a dose effect, our data does not suggest any
22 appreciable advantage for doses above 100 milligrams.

23 I should mention parenthetically -- it was
24 actually in Dr. Dienstag's publication of the U.S. 3-month
25 study and also in a publication in the Annals, in a letter

1 to the Annals in April, doses above 100 milligrams will
2 actually produce a little quicker reduction in HBV viremia,
3 but the proportion of patients who've cleared does not
4 appear to be different and that's an important thought I
5 think. So, we figured the long-term clinical significance
6 has more to do with where do patients get to and what
7 proportion of patients clear, and in that regard, we've
8 seen no difference, no advantage for doses above 100.

9 DR. HAMMER: Ms. Melpolder, do you have any
10 questions?

11 DR. BYE: Could I just make a supplemental
12 comment on behalf of Glaxo Wellcome?

13 DR. HAMMER: Please identify yourself for the
14 transcript.

15 DR. BYE: Dr. Bye, Glaxo Wellcome, Clinical
16 Pharmacology.

17 It's a very interesting question, and what
18 we've found, there was remarkable concordance between the
19 acute model and the long-term chronic therapy, and there
20 was a population analysis done from the data that Dr. Brown
21 was alluding to where we had pharmacokinetic sampling. And
22 we also found this relationship in terms of AUC and effect
23 of around about 4,000 area units.

24 DR. HAMMER: Thank you.

25 Dr. Hollinger?

1 DR. HOLLINGER: Yes. I'd like to, first of
2 all, just comment about the reduction that you were just
3 discussing. With viruses, when you've got hundreds of
4 billions of particles that can be circulating, 99 percent
5 is not a great deal. I mean, it's a fair amount, but
6 you're still left with a very large amount of virus in that
7 population. And that has always been one of the things
8 that has concerned me because the hybridization techniques
9 which are often used have a cutoff somewhere around 5
10 million or so, whereas PCR techniques may be down to less
11 than 100, less than 50 copies per ml. So, I think that
12 that's something that needs to be assessed a little bit
13 better.

14 On the other hand, there may be a cutoff level
15 at which levels have a great deal to do with improvement in
16 histology. It seems to be that way. Could you comment,
17 first of all, about that? Then I need to ask you something
18 else.

19 DR. BROWN: Sure. I mentioned we had two
20 sources of PCR data. One was in the European 6-month phase
21 II study, kind of our last phase II dose-ranging. We did
22 do some PCR analyses in that. There we found no real
23 difference in proportion of patients who cleared --
24 detectable virus at PCR levels of sensitivity at 6 months,
25 and the dosing cohorts there were 25 milligrams, 100, and

1 300. So, even at PCR levels of viremia, we didn't see a
2 dose effect, so to speak.

3 What we did see, however, is when we look at
4 the PCR data we have, as well as the branched DNA data that
5 we have from the pediatric study, we see that on average
6 the viral load reductions with lamivudine, in fact, tend to
7 average 3 to 4 logs. So, it's well over the 99 percent.

8 I mentioned in the data displays you saw, we
9 were kind of artificially limited to a 2-log display
10 because for the purposes of those analyses, just for
11 manipulating the numbers, we arbitrarily assigned an
12 undetectable value. We assigned it a value of .8 picograms
13 not knowing what the real viral level might be, of course.
14 So, in fact the antiviral effect is more like 3 to 4 logs,
15 what you might call 99.9 percent on average.

16 DR. HAMMER: If I may, what's the lower limit
17 of sensitivity on the PCR assays?

18 DR. BROWN: Yes. We were using an assay that
19 typically had a sensitivity of 1,000. Some labs will
20 advertise 10 or 100. We feel we had a consistent 1,000
21 detectability.

22 I'm not sure if I answered the entire question.
23 If you would remind me of the second half of your question.

24 DR. HOLLINGER: I saw that in here where you
25 said you used .8 picogram. I was under the impression that

1 1 picogram --

2 DR. BROWN: .8 picogram.

3 DR. HOLLINGER: -- is about 300,000 copies per
4 ml.

5 DR. BROWN: Right.

6 DR. HOLLINGER: Yet, the hybridization assay
7 has a lower level of detection of 5 million. So, I'm not
8 sure why .8 was used instead of more than that.

9 DR. BROWN: That was just a convention we
10 adopted. The threshold of detection, the lower limit of
11 detection of that assay is thought to be on the order of
12 1.6 picograms per ml. So, we arbitrarily assigned a value
13 of half that to the undetectables.

14 DR. HOLLINGER: Yes. Again, I'm not sure why
15 1.6. Maybe somebody could help me. We've always used that
16 1 picogram was around 300,000, so 1.6 would be around
17 500,000, not 5 million which would be closer to 10
18 picograms in there.

19 DR. BROWN: Right. The kit had a fair amount
20 of data behind the kit to suggest a threshold of 1.6
21 picograms. I think you're also alluding to a problem in
22 the area of HBV diagnostics in general which is that
23 there's no real cross standardization, and in particular
24 there are no real known gold standards for serum samples
25 with defined viremia levels by particle counts or some

1 traditional method.

2 DR. HOLLINGER: Scott, if I could ask one
3 other.

4 I think safety is really a key issue here,
5 probably as much as anything. You know the problem with
6 fialuridine and its effect on mitochondrial DNA. I know
7 you mentioned in your information -- very good, by the way.
8 The packet was very nicely put together and very useful.

9 You mentioned about the fact that this is only
10 transiently incorporated into mammalian DNA and that any
11 amount that might be incorporated into the DNA would
12 probably be removed by a 3 prime/5 prime exonuclease
13 activity. Can you go a little bit more into that and tell
14 us why that's the case and what information you had to
15 support the fact this does not act as a chain terminator of
16 the mitochondrial DNA?

17 DR. BROWN: If we might have slide M-75. This
18 kind of summarizes the data for why we feel there are no
19 fialuridine-like effects with lamivudine. I think one
20 obviously would keep in mind as well that fialuridine-like
21 toxicities, if they're mediated by mitochondrial damage,
22 would of course be appreciated as general toxicities that
23 would occur fairly commonly in a patient population and, as
24 was seen with fialuridine, might occur with cumulative
25 dosing, but it wouldn't be a rare kind of event because

1 mitochondrial DNA and mitochondrial proteins are well
2 conserved across individuals with minimal polymorphism.

3 So, in any case, the observations that are
4 relevant for lamivudine are, first of all, that the drug
5 has negligible affinity for gamma-DNA polymerase and no 3
6 prime hydroxyl group, and that's what results in the no
7 stable incorporation into mitochondrial DNA.

8 We have done studies and especially a number of
9 external investigators have actually studied lamivudine and
10 other nucleosides with regard to their effects on
11 mitochondrial function, such as glycolytic pathways and
12 oxidative pathways, and lamivudine has been noted, I think
13 in the New England Journal editorial and a few other
14 places, to have no effects on mitochondrial function. In
15 fact, there was a literature report I guess this past June
16 by the Dutch group suggesting that KICA breath testing in
17 hepatitis B patients may actually be improved on lamivudine
18 therapy, and that is thought to be a measure of
19 mitochondrial function.

20 In any case, we've also had some in-house data,
21 in animal based data, that there were no ultra-structural
22 changes in mitochondria in animals treated chronically with
23 lamivudine.

24 The clinical evidence actually, first of all,
25 is that there's no fialuridine-line syndromes observed in

1 the clinical program, no cases of clinical pancreatitis
2 observed in the phase III control data. That may be
3 important. I showed you the data that amylase, lipase, and
4 ALT elevations were similar to placebo. I'm mentioning
5 this because the full-blown fialuridine like syndrome, if
6 you will, comprised pancreatitis, acidosis and elements of
7 liver failure sometimes. So, these are the clinical
8 observations, again backing up the notion that we really
9 don't see any fialuridine-like effects with the drug, but
10 we think these are scientific reasons.

11 DR. HAMMER: Dr. Sjogren, do you have
12 questions?

13 DR. SJOGREN: Thank you, Dr. Hammer. I have a
14 couple of questions for the sponsor.

15 The first one is in patients who received
16 lamivudine for a year, maybe 2 years, and there is no e
17 antigen loss, does the sponsor have a feeling for what
18 happens -- how long can we continue giving lamivudine,
19 especially in patients who may be quite compromised and in
20 which a recurrence of hepatitis B could be quite
21 significant in their clinical outcome?

22 What is the experience in this kind of patients
23 if you stop lamivudine? What is the experience long term?
24 What happens to them clinically and histologically? Do
25 they know?

1 DR. BROWN: This is kind of a limited
2 clarification period, so I won't show you the slides with
3 all the data, so to speak, but let me just mention.

4 We've actually looked at the data for patients,
5 for example, in the composite phase III who did or did not
6 lose e by week 52, and there's clearly a histologic benefit
7 in the patients who don't seroconvert, if you will. We do
8 see histologic improvements in the patients who are still e
9 positive beyond a year, so to speak. So, I think the
10 answer to the first part is we expect to see improvements
11 in liver histology and ALT normalization in those kind of
12 patients on a prolonged basis.

13 I showed you the end of year 2 data in the
14 longest cohort we have, which is the Asian multi-center
15 cohort, where approximately 40 percent of the lamivudine
16 patients had developed detectable variants. If you look
17 within that group at year 2, at week 104, 60 percent of the
18 patients with the variants have normal ALT levels, again
19 some evidence that there will be prolonged benefit
20 obviously with the wild-type that tends to stay suppressed,
21 but as well with the variants. I should say the ALT
22 normalization rate after 2 years in patients with wild-type
23 was 80-plus percent.

24 So, we think patients who don't e convert will
25 continue to have benefit in their liver disease measured

1 histologically, also by ALT levels, and I hope that is a
2 substantial answer to your question.

3 DR. SJOGREN: Another question that I have is
4 it was mentioned that patients with normal ALT were
5 included in one of the phase III trials in the Orient. I
6 wonder if they were able to analyze that data and what kind
7 of conclusions did they draw in patients that have normal
8 ALT and what happens to them.

9 DR. BROWN: Yes, it's certainly possible that
10 the discussion may range over these in the afternoon where
11 you'd want the color slides, but in a nutshell, in patients
12 with normal ALT what we found in this trial program was
13 that the median -- as you mentioned, the cohort is derived
14 essentially from that Asian multi-center trial. It's about
15 a third of the patients in that cohort.

16 The median HAI score at baseline for the
17 subgroup with normal ALT was 5 points. Zak has sort of
18 told me indirectly that any one of us might have score up
19 to about 3, but 5 is probably abnormal. We were able to
20 measure histologic response in 44 percent of patients with
21 normal ALTs. So, a patient who just has one cross section
22 of value at normal ALT may not represent the true, healthy,
23 long-term healthy carrier, and there's literature from the
24 late 1970s to suggest that if you just have a cross
25 sectional analysis of a population and look at people with

1 normal ALTs, roughly 40 to 50 percent of the patients will
2 have some underlying liver inflammation. I think that data
3 is very similar to what people have found in hep C blood
4 bank based studies.

5 DR. HAMMER: I'll just interject if there's a
6 key slide that you wish to show to answer questions, please
7 do.

8 DR. BROWN: I gave the numbers off the key
9 slide.

10 DR. SJOGREN: What about e antigen loss in that
11 kind of patient, in the ALT normal? I understand that
12 histologically it may be difficult to make a very clear
13 point as compared to your chronic hepatitis patients, but
14 the e antigen loss in those patients -- what did it look
15 like?

16 DR. BROWN: Right. We've done some subgroup
17 analyses and some regression modeling. You do see higher
18 rates of e antigen loss progressively with higher and
19 higher ALTs, just as you do with interferon, although I
20 will say the association with lamivudine may not be quite
21 as tight because it's not always a statistically
22 significant association. But even in the low group with
23 less than twofold elevations at baseline, we do see a rate
24 of e loss that may be a bit above placebo. The actual
25 numbers, at less than twofold elevation, I think it was 12

1 percent. This is the histologic response I mentioned
2 earlier, but 11 to 12 percent of patients with ALTs below 2
3 will lose e compared to a placebo rate of 5 percent. So,
4 with large enough studies, you probably could measure an
5 effect. With absolutely normal ALTs, e conversion probably
6 is the factor that's most influenced.

7 DR. HAMMER: Dr. Lee.

8 DR. LEE: Thank you, Mr. Chairman.

9 I'd just like to make a comment about one of
10 your key phase III studies and then ask for your responses.

11 The B3010 active control study. First of all,
12 the histology appeared worse in the combination group
13 treated with lamivudine and interferon than lamivudine
14 alone, but I think the timing of the second biopsy done
15 while people were still on lamivudine treatment versus in
16 the combination group, having been off treatment for 28
17 weeks, makes that data very, very difficult to interpret.
18 It would only be logical that someone still on the active
19 treatment would have a much better histology.

20 The second thing is I think many of us in the
21 hepatology community were disappointed at the outcome and
22 the design. It appeared that the 29 percent e antigen
23 seroconversion rate in the combination group might have
24 been statistically significant if the study had been
25 sufficiently powered with a bigger sample size. Certainly

1 I remain unconvinced that the combination isn't the way of
2 the future, and I'd like to hear the company's comments.

3 DR. BROWN: Sure. Maybe we should start with
4 slide M-35.

5 This is the direct comparator study, which has
6 just been referred to, the European/Canadian multi-center
7 study. Here we're showing not just the proportion of
8 patients whose histologic activity index improves by 2
9 points or more, but also the proportion of patients in whom
10 it worsens by 2 points or more, indicated down here. The
11 other patients are patients whose change in HAI score was
12 less than 2 points, and those would be on the 0 change
13 line. So, let me first comment on the sort of histologic
14 differences, if you will.

15 We showed you in a sense the above 0 change
16 line results on previous slides in this particular display
17 instead of the conservative display of all missing data's
18 nonresponders. We just excluded them from the analysis.

19 So, here you see the results for lamivudine
20 monotherapy on that trial for the reduction in Knodell HAI
21 score. You see the actual distribution of change, if you
22 will, by 2-point categorical changes clearly shifted in the
23 right direction for lamivudine.

24 This is the interferon monotherapy arm here
25 where just speaking arithmetically, so to speak, a higher

1 proportion of patients on interferon monotherapy seemed to
2 worsen.

3 This is the result you alluded to. This is the
4 distribution of histologic change in the combination arm
5 for the overall change in total HAI, a bit of a shift above
6 the 0 change, but not as impressive as perhaps either of
7 the other two.

8 So, what does this say? It doesn't necessarily
9 mean that more patients worsened. It just means that, in a
10 sense, in this particular study fewer patients improved.

11 Here's the change in fibrosis, and this is sort
12 of the distribution of change in fibrosis. This is done by
13 the so-called ranked assessment because we felt that the
14 discontinuous 4-point scale, so to speak, in the Knodell
15 might not be the right way to go in this kind of analysis.
16 So, these are the blinded ranked assessments that Dr.
17 Goodman alluded to. It looks at both slides and
18 arbitrarily decides -- or I should say studies the slide
19 and decides which slide looks better and assigns a score to
20 that, and then which slide looks worse, and then unblinds
21 treatment eventually in the end once all the readings are
22 done.

23 What we see here is for the prevention of
24 fibrosis -- or I should say for the proportion of patients
25 who have improved in fibrosis versus worsening. We showed

1 you some of the worsening comparisons. In particular, in
2 this study the comparisons of lamivudine to the other two
3 treatment arms -- there was a trend in a sense. The 3
4 decimal p value of this comparison was .051, but that was
5 not a statistically significant result.

6 Here's the fibrosis result for the combination.

7 So, my sense of this data is there's no clear
8 advantage histologically for combination.

9 I should briefly mention the other principal
10 results from the study.

11 For ALT normalization, ALT normalization was
12 significantly best and significantly better for lamivudine
13 monotherapy compared to either interferon or combination.
14 So, yes, the e loss and e conversion rate, so to speak,
15 which you saw in the slide were a proportion higher, but
16 they were not statistically significant in the intent-to-
17 treat and there were some disadvantages or lack of other
18 advantages for combination. But I think we all agree that
19 combination regimens in the right setting and perhaps other
20 kinds of designs in the future with interferon even might
21 be worth studying. But this particular design did not
22 produce any clear advantage, and of course, there were some
23 safety offsets that I did review.

24 DR. HAMMER: Dr. So?

25 DR. SO: Thank you, Mr. Chairman.

1 I have a few questions. The first one is can
2 you comment on your incidence of loss of B surface antigen
3 at 1 year and 2 years? Because based on the information
4 you have provided on the book, I made some quick
5 calculations, and it seems like at the end of 1 year
6 patients who were treated on lamivudine had an incidence of
7 B surface antigen loss of 1.5 percent, whereas the patients
8 who were treated with lamivudine and interferon, the
9 incidence was 3.4 percent at 1 year. Do you have any
10 further information?

11 DR. BROWN: Yes, slide M-49.

12 This is the overall observation regarding s
13 antigen loss, which I think we're all interested in because
14 it may represent in a sense ultimate clearance of the
15 virus, although even patients who are anti-s positive and
16 have never had active disease can be reactivated under
17 conditions of debilitation. So, s antigen loss is not a
18 perfect marker of cure, but it's pretty good.

19 This is the overall s antigen loss observation
20 for phase III. If you look at the sort of comparative
21 data, the direct comparison was in that European/Canadian
22 multi-center study. What we saw was 3 patients on
23 lamivudine 100, 3 out of 82, lost s. On the combination
24 arm, it was 2 out of 75, and on the interferon it was 2 out
25 of 69. So, indistinguishable in the head-to-head

1 comparisons at 1 year.

2 There was sporadic s loss elsewhere in the
3 program illustrated here.

4 Perhaps interestingly, even though I think the
5 bottom line on this has to be that the s loss numbers are
6 quite low across the program, but perhaps interestingly
7 there were no patients treated with placebo throughout
8 phase III who lost s, and all the sporadic s loss occurred
9 on the other treatment assignments.

10 But if you take these kind of percentages in
11 parentheses for the various treatment assignments and in
12 particular probably the most important thing is the head-
13 to-head comparison. These are the treatment-naive studies,
14 by the way, and this is the interferon nonresponder
15 population who may in fact have some biologic differences.
16 But in any case, we didn't see an appreciable treatment-
17 related difference, and obviously to statistically measure
18 any differences there would need a very large sample size.

19 DR. SO: What about the 2-year follow-up in the
20 Asian study?

21 DR. BROWN: Well, actually interestingly
22 enough, I didn't point it out here, but as you might have
23 guessed from the New England Journal article as well, it
24 did appear that s loss was a bit more common in the
25 sporadic observations that we had. There was actually no s

1 | loss in the first year in the Asian multi-center trial
2 | published in the New England Journal.

3 | Actually, I might turn to Frasier. I don't
4 | know if we have any s loss in year 2. So, it's still low
5 | or 0 in year 2 we think.

6 | I didn't actually mention this. We could get
7 | into it this afternoon. What we see in Asians versus
8 | westerners, there's a similar full e conversion rate at 1
9 | year, but a little higher e loss rate at 1 year in the
10 | westerners. There may be a subtle difference here in s
11 | loss where the sporadic kind of s loss we see may be a
12 | little more common in western populations. That would be
13 | actually sort of similar to what you might expect from a
14 | reading of the epidemiologic literature on just patients
15 | who naturally e or s convert.

16 | DR. SO: So, as Dr. Lee said, I think it's
17 | still worth studying the effect of combination therapy with
18 | interferon to try to increase the incidence of surface
19 | antigen loss in that population.

20 | DR. BROWN: Right, and we'd probably agree.

21 | DR. SO: The other comment is you mentioned you
22 | were thinking of using hepatitis B e antigen seroconversion
23 | as a target endpoint for treatment.

24 | DR. BROWN: Right.

25 | DR. SO: I guess this is based on the European

1 long-term follow-up of patients who were treated with
2 interferon, and after 5 years, patients who seroconverted
3 seemed to have a lower incidence of complications of
4 cirrhosis or hepatocellular carcinoma. Is that right?

5 DR. BROWN: Are you referring to the Niederal
6 paper in the New England Journal?

7 DR. SO: Yes.

8 DR. BROWN: Yes. I think the principal finding
9 out of that was that the loss was, in terms of the data they
10 could measure, the variable that was most associated with
11 better long-term outcomes.

12 DR. SO: I have some concern from my colleagues
13 in Asia, especially from Hong Kong, where they followed
14 close to 1,300 patients with chronic hepatitis B, and they
15 found about 68 percent of the patients who eventually
16 developed complications of cirrhosis such as bleeding,
17 ascites, and also hepatocellular carcinoma were actually
18 anti-HBe antibody positive.

19 So, the endpoint of treatment may be much
20 further than just seroconversion. I think you really need
21 much longer follow-up and treatment to assess whether it
22 makes an impact on lowering the incidence of complications
23 of cirrhosis or reducing the risks of hepatocellular
24 carcinoma.

25 DR. BROWN: Right. You may be referring too to

1 a clinical phenomenon, the so-called precore mutants, where
2 patients with precore mutant virus, of course, can be e
3 negative/anti-e positive, but in fact have high viremia
4 levels or middle to high viremia levels, I should say.
5 What we've run into in running this development program is
6 that the data on precore mutants appears to be a lot more
7 extensive in southern Europe, for example, than it is in
8 Asia, although you can see in the literature that precore
9 mutant or anti-e positive hepatitis B is in fact thought to
10 be reasonably common out there. We're actually doing a
11 kind of an epidemiologically based molecular study, if you
12 will, to try to look at the prevalence of precore mutants.

13 But that phenomenon of a patient with active
14 virus replication who's anti-e positive is often due to
15 precore and core gene mutations in the virus which don't
16 seem to affect its pathogenicity. Some studies suggest it
17 may even be a little worse.

18 We did conduct a study in Europe in about 126
19 patients with precore mutant hepatitis B, and that result
20 was actually reported in the spring. The antiviral effects
21 in those patients appeared to be quite good. The
22 difficulty there is you can't measure e loss because
23 they've already lost e. So, that kind of phenomenolgy is
24 mixed in with the other phenomenon that you're referring to
25 I think which is some patients will develop advanced

1 disease and may seroconvert around the same time, and so
2 they can seroconvert. But it happens to have happened or
3 may even accelerate in some cases their cirrhosis
4 development. That kind of patient can have a poor outcome
5 even though they're anti-e positive.

6 DR. SO: Actually the study I refer to is from
7 Hong Kong, and they found that about most of the patients
8 in that population -- if they seroconvert to anti-HBe
9 antibody positive, they were like at a median of 35 years
10 of age, and they developed complications of cirrhosis and
11 hepatoma at the age of about 43 years of age.

12 But since the primary target population is
13 going to be a lot of Asians, just shooting for target
14 endpoints for seroconversion might not be adequate. It
15 might have to be given long term to really see whether it
16 makes an impact.

17 DR. BROWN: Yes. Certainly we're going to be
18 looking at some long-term benefit and have designed a
19 fairly substantial, what we hope will be a phase IV study
20 to look at long-term clinical benefits.

21 The way we try to differentiate those patients
22 who are anti-e positive and what their outcome might be is
23 to use DNA assays. A lot of the patients with precore
24 mutants will have detectable DNA, whereas the patients who
25 are going to do well will be the patients who are e

1 negative but also DNA negative. That's in fact why we
2 linked the DNA analysis into our e conversion. In a sense,
3 it serves as a way to screen out patients who may have
4 developed precore mutants.

5 DR. HAMMER: Thank you.

6 Dr. Stanley?

7 DR. STANLEY: Thanks.

8 Just a quick follow-up to Dr. Lee's concerns
9 about NUCB3010. Not only are you comparing patients being
10 treated with those off treatment for a while, but the
11 combination patients only got 24 weeks of lamivudine
12 compared to the 1 year. What was the rationale for that?

13 DR. BROWN: I should first thank Schering
14 Plough for supplying the interferon alfa-2b.

15 That was actually a design that was used in the
16 U.S. multi-center trial. The feeling on if they got
17 interferon treatment was that the maximum benefit in B --
18 and this may or may not be true for C -- so, there are
19 differences in these two hepatitises. But the maximal
20 benefit in B with interferon therapy does not appear by end
21 of treatment. It actually appears that patients will
22 continue to experience some seroconversion out to about at
23 least 6 months post-treatment.

24 So, if you look at the design of the U.S.
25 multi-center trial that Dr. Perrillo published in the New

1 England Journal or if you look in the U.S. label for Intron
2 A, you'll see that in fact the primary assessments for both
3 virologic response and histologic response were 6 months
4 post treatment. The feeling is at the end of treatment --
5 and Dr. Perrillo is here, if you want to comment -- many of
6 the good responders to treatment may actually be
7 histologically flaring. So, the histologic results at end
8 of treatment in B are not necessarily as good on interferon
9 as they are 6 months later. So, that was one of the main
10 reasons I think why the advice to put the primary
11 assessment 6 months post-treatment for interferon was
12 incorporated into the trials.

13 DR. STANLEY: But I'm specifically asking why
14 the lamivudine was limited to 24 weeks because you've shown
15 in other patients that post-lamivudine, they may have a
16 bump in ALT anyway.

17 DR. BROWN: Right. That's a scientific design
18 question. I mentioned briefly that really what we were
19 trying to investigate there was, does pre-reduction of
20 viral load with lamivudine for 8 weeks allow an enhanced
21 seroconversion rate with the interferon, and we wanted, of
22 course, keep viral load low during the interferon treatment
23 as well. That relates back to some data that Dr. Perrillo
24 and others published that patients with viral loads above
25 200 picograms or so don't respond well to interferon. So,

1 the thought really in this collaborative effort was that if
2 we pre-reduced viral load, we may get enhanced
3 seroconversion.

4 I think the designs that many people are
5 thinking about nowadays are to continue lamivudine and
6 piggy-back an interferon and see if that might produce a
7 better effect. We don't have that measurement available.

8 DR. HAMMER: Thank you.

9 Dr. Yogev.

10 DR. YOGEV: Thank you.

11 I would like to ask a couple of questions about
12 the pediatric and adolescents. First of all, how many
13 adolescents were in the studies?

14 DR. BROWN: Let's see. We have that number,
15 but it might be easier just to get it from somebody who has
16 got it memorized. There were 53 total patients. How many
17 adolescents? 14 or 15. We could dig it out of the slide
18 if you need it.

19 DR. YOGEV: The reason I'm asking is at least
20 from data you submitted, it seems like that they did not
21 respond as expected in a dose which is the adult. They
22 were much less good. Any explanation for that? Are you
23 planning to do more adolescents?

24 DR. BROWN: Right. Actually their response was
25 quite good and I think we can show you that response. I

1 think we have it coming shortly, the pediatric DNA
2 response.

3 This is some data from that study. This is
4 actually the baseline DNA and ALT in the dosing groups in
5 the pediatric study. I think what we want to do is skip
6 ahead to the DNA response graph.

7 The primary virologic method in this study was
8 the branched DNA assay, although we did also do PCR as
9 well. We haven't unfortunately broken out the adolescents,
10 but here you can see the similar kind of very marked
11 antiviral effect at 2 weeks, patients essentially clearing
12 in the Chiron assay. I don't recall there was a
13 substantial difference for the adolescent patient subgroup,
14 but perhaps Dr. Dent or Dr. Gray would want to comment
15 briefly.

16 The next slide may have the log decrease. Yes.
17 Again, but this is not broken out by adolescents. I'm
18 sorry. There it is, the 100 mg dose, yes. Essentially
19 this is probably due to fairly small sample sizes and
20 sampling error. I don't think we appreciated that it was a
21 significant difference, if you will.

22 Here's a good example of the kind of
23 phenomenology that Dr. Hollinger alluded to in some
24 respect. Using a more sensitive assay with a wider dynamic
25 range, we do see a 3 log reduction on average, but that's

1 using a more sensitive assay.

2 I think in these kinds of cohort sizes, these
3 kinds of treatment differences -- using the AUC data and
4 the antiviral effect, one can appreciate that through that
5 kind of effort that there is a dosing difference. But in
6 terms of proportion of patients who clear in adolescents as
7 a subgroup, I don't think we really appreciate the
8 significant difference because of the sample size.

9 DR. YOGEV: And the study was only for 4 weeks?

10 DR. BROWN: Right. This was a dosing cohort
11 study. Actually I guess we can say we've initiated at this
12 point a large phase III multi-center study in children, an
13 international study in North America and Europe.

14 DR. YOGEV: I noticed that you used the 2-point
15 score of Knodell as the one to assure a major change. And
16 yet, the hepatologist was mentioning that you can have that
17 change. It depends what you eat in the morning. I just
18 wonder, what would be the intra-pathologist difference?
19 Would it be more than 2 or 3 points?

20 DR. BROWN: Yes. The typical change on the
21 lamivudine treatment groups, the change in median scores
22 for the group as a whole, was typically 3 to 4 points or
23 more, but the change in median score was typically 3 to 4
24 points for lamivudine.

25 The 2-point categorical response definition is

1 | essentially quite consonant with what's been recommended in
2 | hep C trials by the NIH consensus conference. The
3 | difference there is last year they recommended subtracting
4 | out the fibrosis score, if you will, and measuring changes
5 | in necroinflammatory response, the sum of the first three
6 | components. So, we did actually do that in our program,
7 | and I didn't highlight it on my slide, but there were
8 | significant changes in the categorical approach to that
9 | kind of data, using 2-point or greater change as
10 | recommended for hep C trials. But as I mentioned, this
11 | change in median scores tended to be on the order of 3 to 4
12 | points, which might be more clinically --

13 | DR. HAMMER: The question that Dr. Yogev raised
14 | about inter-pathologist variation, which came up in one of
15 | your studies?

16 | DR. BROWN: I think, as Dr. Goodman tried to
17 | point out, when there's, if you will, that kind of subject
18 | of a random variation, that would actually obviate against
19 | observing a treatment effect in large trials. So, as Dr.
20 | Goodman pointed out, that's the power of doing large
21 | controlled trials, is to see this kind of treatment
22 | difference between two groups.

23 | DR. HAMMER: Thank you.

24 | Dr. Hamilton?

25 | DR. BROWN: I should add one other comment.

1 I'm sorry, Dr. Hamilton.

2 The reason we adopted a categorical response
3 definition goes back to some early trials where differences
4 in means for response were thought to be potentially
5 clinically meaningless. For example, in some of the early
6 trials, there was a .7 difference in mean scores for
7 treatment groups, and that was thought to be perhaps not
8 terribly clinically relevant.

9 So, it was thought more appropriate to define
10 some kind of categorical response that patients might
11 achieve and might be clinically significant and then
12 measure that as a categorical phenomenon because if you do
13 very large studies, of course, relatively small differences
14 in means may become statistically significant, and yet that
15 may not be clinically significant. So, that's why you
16 adopted these kind of categorical response definitions.

17 DR. HAMMER: Were the pathologists blinded
18 to --

19 DR. BROWN: Yes.

20 DR. HAMMER: They were blinded to the
21 treatment. Were they blinded to the patient over time?

22 DR. BROWN: Yes. In trying to cut down the
23 data from 40 trials to a relatively brief presentation, I
24 removed one slide that emphasized that these studies were
25 all done with the central independent pathologist blinded

1 with regard to the slides, with regard to treatment,
2 patient identification, date, and sequence. They didn't
3 know which was the baseline and which was the follow-up
4 slide.

5 DR. HAMMER: Dr. Hamilton.

6 DR. HAMILTON: Yes. I'd like to reciprocate
7 for the clinician-friendly slides by asking only really
8 easy questions here this morning.

9 (Laughter.)

10 DR. BROWN: We are most grateful.

11 DR. HAMILTON: A nuts and bolts question first.
12 I added up a few of the columns and a few of the rows on
13 some of the slides to try to come up with a sense of lost
14 to follow-up, missing pieces of data, dropped out,
15 disappeared, whatever, and I didn't actually satisfy myself
16 about that point. Could you speak to that point?

17 DR. BROWN: Right. In the overall program, we
18 actually found that we had very good retention of patients.
19 Typically at least 80 to 90 percent of patients completed
20 the study. Overall, the highest study completion rate was
21 in fact in the Asian multi-center trial. I think it was on
22 the order of 96 percent. So, we had quite good patient
23 compliance throughout these studies.

24 With regard to the impact on the data, probably
25 one of the key slides to look at would be in the core, but

1 it would be the study, the subanalysis I showed of the 2-
2 year Asian cohort carried forth for ALT and DNA data.

3 We've looked at that in some detail now, and
4 that kind of stabilizing or trending downward, if you will,
5 of the DNA and ALT values in the patients with the variants
6 does not appear to be due to patient dropout. In fact, we
7 lost 25 patients in that year of additional follow-on in
8 the 3018 study. The reason we lost 17 of those 25 was that
9 they were seroconverted and found to need no further
10 treatment. So, 17 dropped out for e antigen conversion,
11 and we looked at the 25 with regard to were they variants
12 or not, and none of those were identified as variants at
13 the week 52 analysis leading into their year of additional
14 study. So, we don't think dropout phenomena account for
15 that critical analysis that we showed you of the 3018 data.

16 As I said, in the overall program, the
17 compliance of patients was excellent and a very high
18 completion rate. If you look at the proportion of patients
19 who actually got both biopsies, it was quite high compared
20 to some of the earlier clinical trials in hepatitis B and C
21 patients where as many as 30 or 40 percent of patients
22 didn't have the paired biopsy comparisons. We typically
23 had 80-plus percent of patients available with both
24 biopsies.

25 DR. HAMILTON: A second question concerns the

1 possible difference, if any, in response in those patients
2 who acquired their disease as adults or as infants. Having
3 an Asian cohort, you might have an exceptional opportunity
4 to examine that question, and I wonder if you did.

5 DR. BROWN: Well, some people in the room know
6 I was trained as a pediatrician. So, the approach we've
7 taken in pediatrics has been initially to emphasize those
8 children who have active disease, not the kind of high
9 viremic carriers that are found especially in the
10 developing world. But I will say that the antiviral
11 effects we expect to see about the same. We've taken an
12 approach to active disease in children because we think
13 those are the kids who most need it. As we evolve more and
14 more lamivudine data, I think we'll appreciate what the
15 effects are in what you might call high viremic children
16 with normal ALTs who are quite common worldwide.

17 I don't know if that answers your question, Dr.
18 Hamilton. That was your toughest question. You promised
19 they'd all be easy, but if I can clarify that one, I'd be
20 happy to.

21 Oh, differences in disease between vertical and
22 horizontal?

23 DR. HAMILTON: Yes.

24 DR. BROWN: Yes, okay, sorry.

25 I alluded a little bit to our observations.

1 What appears to be the case in the integrated data set is
2 that the e loss rate at 1 year is about 30 percent for
3 caucasians, if we just limit ourselves so that we have
4 defined ethnic groups. In caucasians, the e loss rate at 1
5 year was 30 percent compared to 20 percent in Asians, but
6 if you talk about a gain of anti-e and, of course,
7 maintenance of undetectable DNA, the seroconversion rate
8 was not appreciably different between Asians and
9 caucasians. So, it may be that we'll see a little higher
10 seroconversion rate in the caucasians as they go into year
11 2, as they gain anti-e and that sort of thing. So, that
12 was one subtle difference.

13 We did not see any difference in responsiveness
14 to lamivudine with regard to histologic responses, for
15 example, and there are colorful slides to show that.

16 We didn't see any difference with regard to ALT
17 normalization. We have a number of regression models in
18 which we looked at various safety and efficacy phenomena.

19 So, I would say the principal observations are
20 a little higher e loss rate in caucasians compared to
21 Asians at 1 year, but no real difference in seroconversion.
22 I think the overall rate was something like 17 percent of
23 Asians fully seroconverted compared to 18 percent of
24 caucasians, not statistically different in the overall
25 program. So, there may be something interesting going on

1 | there.

2 | DR. HAMILTON: Finally, in adults with acute
3 | disease, do you have any data?

4 | DR. BROWN: No. The real problem there we run
5 | into I think is one I think everybody can appreciate.
6 | Especially in the West, the clinical recognition of acute
7 | hepatitis B is increasingly rare, and so it's extremely
8 | difficult to set up kind of a large-scale controlled
9 | protocol designed to find those patients.

10 | The other key study design obstacle that we run
11 | into is trying to think about -- the primary endpoint would
12 | obviously be to try to prevent transition to chronicity or
13 | perhaps to have some impact on the acute disease. The
14 | latter is fairly easy if you can find the patients, but if
15 | transition to chronicity in adults is more like -- I think
16 | the more modern data would suggest 2 to 8 percent of adults
17 | might be chronic disease -- then trying to show a treatment
18 | effect on a 2 to 8 percent event rate requires very, very
19 | large sample sizes in a patient population that's difficult
20 | to find in the first place. So, that's why we haven't yet
21 | really been able to study acute hepatitis B although we
22 | have some goals to try to figure out a way to do so,
23 | perhaps through large networks.

24 | DR. HAMMER: Thank you.

25 | Dr. Diaz?

1 DR. DIAZ: It's a little bit different question
2 but along the same theme. Within a particular study, were
3 you able to in any way look at the placebo group compared
4 to the treatment group and break it down in terms of length
5 of time patients in each of those groups had chronic
6 disease, in other words, how long they had changes, for
7 instance, in their ALT over time, how long they perhaps had
8 had other maybe histologic evidence of disease and compare
9 those two?

10 DR. BROWN: Right. We did have a question in
11 the case rec forms having to do with what you might call
12 recognized duration of disease, and we didn't really see
13 any substantial differences in that in across treatment
14 groups.

15 The real problem with this kind of data might
16 have been highlighted by that baseline -- I guess it was
17 the disease-associated phenomena I showed, the routes of
18 transmission. It appears that worldwide the single most
19 common route of acquisition is unknown. Most patients
20 don't know when and how they got their hepatitis B, and
21 therefore the duration of infection is unknown and, of
22 course, duration of the underlying liver disease is,
23 therefore, also unknown. But we did have a question of
24 duration of recognized liver disease, and it didn't appear
25 to differ across treatment groups. But since it didn't, we

1 can't really measure an effect. It's an important
2 question.

3 DR. DIAZ: I realize the difficulties in
4 sorting that out, but I wondered if you had any particular
5 data.

6 DR. BROWN: We don't really because of those
7 difficulties.

8 DR. DIAZ: Likewise, on a different theme, not
9 being a pathologist, I too kind of struggle a little bit
10 with a scoring system that has a lower limit of
11 significance set at a change in 2 HAI and yet recognize the
12 consensus panel felt that would be significant.

13 You had different pathologists scoring at
14 different centers. Correct? Was there any attempt to
15 switch slides amongst centers to validate scoring systems
16 between pathologists or, more importantly perhaps, to have
17 the same pathologist rescore the same slides multiple times
18 to validate their reliability of coming up with the same
19 score or within 1 HAI score?

20 DR. BROWN: Yes. We certainly initially took
21 kind of an exploratory look with -- Dr. Goodman may recall
22 -- I think it was 25 or 50 slides. There seemed to be a
23 reasonable correlation in a two and three pathologist
24 comparison, but it certainly wasn't in the very, very tight
25 range and that's very typical of what you see in the

1 literature.

2 So, the most important way in a sense to
3 eliminate observer variation is to have an independent
4 pathologist for each study and have them evaluated not at
5 local pathology labs, so to speak, but by somebody who's
6 trained and experienced with the scoring system which, of
7 course, is not one that's in everyday use in the clinic.
8 So, that has I think been established in the literature as
9 well as an important way to reduce variability here.

10 But the way to reduce inter-observer
11 variability is again to have at least within the study one
12 pathologist look at all the slides, and that's the route we
13 chose.

14 But as you saw, actually in the comparison, we
15 were actually rather surprised. I showed you the primary
16 histologic response data for the three placebo-controlled
17 studies, and that was two different pathologists I guess,
18 and the rankings for both drug and placebo were amazingly
19 consistent.

20 DR. DIAZ: Right. Just a couple of quick
21 questions.

22 On the one slide that you showed for post-
23 treatment ALT elevations where there was a difference
24 between the lamivudine and placebo for ALTs over 3 times
25 baseline or those that were over 500, in particular is

1 | there any correlation between those post-treatment levels
2 | and pretreatment levels?

3 | DR. BROWN: I think the answer to that is no,
4 | but we probably haven't looked at that rigorously enough.

5 | DR. DIAZ: I'll save my questions.

6 | DR. HAMMER: Dr. El-Sadr?

7 | DR. EL-SADR: I have a couple of questions. I
8 | think the first one that probably has a very simple answer
9 | is, why do we use this drug twice a day in HIV and once a
10 | day in hepatitis B?

11 | DR. BROWN: Well, that is a very interesting
12 | question. I think somebody like Dr. Hollinger who is both
13 | a clinician and a virologist could perhaps reflect on this
14 | as well.

15 | But what we think is happening is, first of all
16 | -- we actually published, based upon some of the early
17 | phase II data, a paper in PNAS in collaboration with some
18 | Oxford statisticians. In the UK project, we published a
19 | paper on the viral dynamics of hepatitis B, and sort of by
20 | implication, in comparison to HIV. So, hep B is a rapidly
21 | replicating virus, as everyone knows, but overall probably
22 | slightly slower than HIV. It probably has a little longer
23 | half-life in the body, not very long but a little longer
24 | than HIV.

25 | If you combine that kind of virologic

1 | phenomenology with the long intracellular half-life of the
2 | drug and the reasonable serum half-life, the long and the
3 | short of it is, when we measured HBV DNA effects with
4 | b.i.d., once daily or twice daily dosing, in phase II -- I
5 | didn't highlight that, but we didn't actually see a
6 | difference in terms of our ability to maintain undetectable
7 | DNA levels.

8 | Then Dr. Bye and Dr. Johnson, our clinical
9 | pharmacologists, have done extensive modeling, and we feel
10 | that even with this kind of once-a-day dosing regimen, we
11 | can maintain drug levels in the trough that are
12 | consistently above the IC50 of the virus. So, that's
13 | another aspect of our dosing regimen, if you will, is to
14 | try to keep the levels above the IC50 of the virus, but we
15 | can do that with once-a-day dosing. The clinical
16 | observations are there was no difference between b.i.d. and
17 | q.d. dosing.

18 | DR. EL-SADR: That's in short-term studies.
19 | Right?

20 | DR. BROWN: Well, this was actually, sure, up
21 | to several months of dosing. The principal observation was
22 | at 1-month dosing. That's correct.

23 | DR. EL-SADR: The other question is going back
24 | to I think Dr. Hamilton's question, you implied that about
25 | 20 percent or so of patients had missing follow-up liver

1 biopsy for your primary endpoint.

2 DR. BROWN: Correct.

3 DR. EL-SADR: Was that equal in the placebo and
4 the active group?

5 DR. BROWN: Right. It was essentially equal
6 across treatment groups. We actually did a number of
7 analyses to look at that, as well as adjustment for
8 baseline covariates, and there was still a highly
9 significant histologic effect, if you will in the phase III
10 data.

11 DR. EL-SADR: Did you try to look at this by
12 sort of assigning the missing biopsies as failures or
13 something?

14 DR. BROWN: Yes.

15 DR. EL-SADR: The same question I have as well
16 for the other parameters that you looked at for efficacy
17 because it seemed like all the missing data are imputed as
18 last observation carried forward.

19 DR. BROWN: Well, let me mention two things. I
20 thought the slide I showed in the core for the primary
21 histologic response was with missing biopsies counted as
22 nonresponders. It was in the core, but it was a little
23 subheader that I didn't feature when I reviewed the slide.
24 But in fact, the data you saw was with missing biopsies
25 counted as nonresponders. Here you see it here.

1 DR. EL-SADR: It says here in the one we have
2 that patients lacking either biopsy were excluded. Oh, I
3 see. That's a different one.

4 DR. BROWN: This is the primary response in the
5 placebo-controlled. Histologic response was the primary
6 endpoint in these three studies. In this display, all the
7 missing data, the patients are counted as nonresponders.
8 It was actually significant in both analyses in terms of
9 the statistical testing.

10 The other question actually is an interesting
11 one. We did adopt some conventions for two serologic
12 parameters, e antigen and s antigen, adopted the convention
13 of last observation carried forward. Working with the
14 agency, we also did some additional analyses without that
15 convention. I don't want to presage their discussion, but
16 our sense of those analyses was at least that the effects
17 on e conversion were still there even when you did not have
18 the LOCF conventions.

19 DR. HAMMER: Dr. Masur?

20 DR. MASUR: Do you have data on the safety of
21 the drug in patients with more advanced disease or more
22 active hepatic inflammation?

23 DR. BROWN: Yes. We have the four transplant
24 studies that I mentioned, and we also have a fairly large
25 number of patients on open label compassionate use. The

1 real problem in that setting, as you can imagine, is
2 getting control data. When patients have really
3 immediately life-threatening disease and there's no other
4 agent approved in this kind of clinical setting, it's very
5 hard to get control data. So, I mentioned that we do see
6 more adverse events and more serious adverse events in this
7 population, but when we looked at the pattern, they
8 appeared to be the kind of events you see with the
9 underlying severe liver disease or the surgical
10 complications or immunosuppression. But we can show you
11 all that data, but again it's uncontrolled safety data,
12 kind of observational stuff.

13 DR. MASUR: Just to follow-up on Wafaa's
14 question, maybe I didn't follow exactly what you said, but
15 if the half-life of virus is about the same between HBV and
16 HIV, the intracellular half-life is about the same, for
17 some reason you use 150 milligrams twice a day with HIV.
18 I'm just intrigued as to why there's a difference of
19 approach and whether or not the frequency of resistance
20 might be different with a different dosing regimen or a
21 different dose, if that's clinically important.

22 DR. BROWN: Right. The ability to model half-
23 life, of course, the only ideal way is if you had some kind
24 of therapeutic intervention that would immediately, totally
25 shut down virus replication for HIV or HBV. Those kind of

1 agents still aren't available. The kind of agent you saw
2 here and triple therapy in HIV certainly pretty quickly
3 does so, but as you know, the limitations of these half-
4 life measurements start with that.

5 Accepting that, our modeling efforts so far are
6 that HBV might have a half-life on the order of a day, day
7 and a half, compared to half a day or day or so for HIV.
8 So, that's why I mentioned somewhat shorter.

9 I think the bottom line is within the scope of
10 this clinical program, which is quite large and quite
11 lengthy with regard to some of the study periods, we
12 haven't been able to see a dose effect within the range
13 that we've studied. A dose effect on the incidence of
14 variants, I should say.

15 DR. HAMMER: Thank you.

16 I just have one question. I'm struck by what
17 seems to be a very consistent DNA response, antiviral
18 response, but even after a year of treatment, moderate but
19 proven histologic responses of around 50 percent or so, but
20 even lower serologic responses. I was wondering if that's
21 just a matter of time, or is there something else about
22 limited potency which in fact may be evident by the fact
23 that mutants do emerge?

24 And part of this, if you have the slides on DNA
25 response and also with inter-quartile ranges because one

1 | thing we haven't seen -- we've seen median responses, but
2 | we don't know whether there are some patients who respond
3 | with 4 or 5 logs and others that respond with 1 log or
4 | less. That may help explain the response rates we're
5 | seeing.

6 | DR. BROWN: Okay. Let me try to distill this
7 | one a little bit.

8 | We don't have a quartile display of response,
9 | but in terms of the antiviral response, we do see, as you
10 | mentioned, a very consistent initial antiviral response.
11 | HBV DNA reductions are essentially observed, as far as we
12 | know. Every patient we've been able to study has had an
13 | initial reduction. If they had an appreciable DNA level,
14 | they've had an appreciable reduction.

15 | There is a range in terms of the quantitative
16 | reduction in that initial antiviral response. It's
17 | relatively unusual for patients to not clear below
18 | detectable in the solution hybridization assay, but there
19 | is a small proportion of patients who don't.

20 | Most of the patients are down in the range of
21 | detectability alluded to by Dr. Hollinger, in sort of the
22 | PCR range. Dr. Condor and I occasionally discuss this, our
23 | project virologist. There is some variability in that
24 | range in terms of patient response, but it's relatively
25 | unusual to not clear by the conventional assay.

1 I should say, as was alluded to earlier, that
2 risks for disease progression in the existing literature so
3 far are primarily -- I think Dr. Hollinger actually alluded
4 to this issue -- associated with levels of viremia that are
5 detectable in conventional assays. So, differences in PCR
6 level viremia in HIV are important because there obviously
7 the max studies have shown, even low level virus, you may
8 eventually progress.

9 But in hepatitis B, Dr. Hollinger alluded to
10 the issue that there may be a level of viremia that perhaps
11 is not associated with disease progression, and in the
12 existing literature the DNA effect, so to speak, is
13 measurable and conventional, people who were plus/minus at
14 conventional hybridization assay levels, which tends to be
15 10 to the 5th, 10 to the 6th. So, there is kind of a
16 different disease consideration here in hepatitis B
17 compared to HIV.

18 It's well documented now that many or most
19 healthy carriers actually have appreciable levels of HBV
20 DNA using PCR assays, and also patients who e convert and
21 then go on to do well clinically tend to maintain low level
22 viremia until they eventually clear s antigen, at which
23 time many of those will lose peripheral viremia but still
24 have DNA in the liver.

25 DR. HAMMER: On the DNA PCR assay, what is the

1 range of responses, just approximately? Is it across the
2 population? Is there a 3 log difference in patient
3 responses or is it much tighter?

4 DR. BROWN: Yes. We've seen in two different
5 studies, our median response tends to be around 3 to 4
6 logs.

7 DR. HAMMER: And the lowest?

8 DR. BROWN: Sorry?

9 DR. HAMMER: I'm just asking what the range of
10 response is to try to get some handle on whether there are
11 other predictors of response rates.

12 DR. BROWN: Well, as Dr. Hollinger alluded to,
13 the conventional assay has a threshold around a million, 5
14 million genomes per ml. Most of our patients go below
15 that. So, the range we're seeing tends to be on the order
16 of 10 to the 3 to -- the range of response tends to be down
17 from wherever they started, which is typically 10 to the
18 7th, 10 to the 8th or above. Typically patients are going
19 down to 10 to the 3 to 10 to the 5 range.

20 DR. HAMMER: Just one last question. In the
21 briefing book, there is a multivariate modeling predicting
22 outcome and lamivudine treatment was the key issue there.
23 But have you looked at both baseline factors and early
24 response factors -- you may have and I may have missed it
25 -- as predictors of response? Because otherwise, it

1 doesn't really -- we have no reason to predict who are the
2 50 percent responders.

3 DR. BROWN: Right. We've looked at baseline
4 factors quite extensively, and time permitting, we could
5 get into that perhaps this afternoon on an individual issue
6 basis. We've not looked at early response factors, but
7 that's certainly something that's worth looking at as we
8 accumulate more and more data. And we are starting to use
9 some of the newer assays in our program as well to give us
10 some of that sensitivity in the lower range.

11 DR. HAMMER: Thank you very much. We
12 appreciate your indulgence with us and our questions.

13 We're running a little bit behind. We'll take
14 a 15-minute break and reconvene at 11:00.

15 (Recess.)

16 DR. HAMMER: We're going to continue now with
17 the FDA presentation. I believe it's going to be headed by
18 Dr. Styrt.

19 DR. STYRT: I'm Barbara Styrt. I'm the
20 clinical reviewer for this new drug application and I'd
21 like to briefly introduce the FDA presentation for NDA
22 21-003 and 004, lamivudine for treatment of chronic
23 hepatitis B.

24 As you're aware, the applicant has submitted
25 results from four principal phase III controlled studies

1 using a 100 milligram per day dose of lamivudine for 52
2 weeks. In this presentation we will refer to the U.S.
3 study, a placebo-controlled study with a 16-week post-
4 treatment follow-up period; the Asian study, a placebo-
5 controlled study using two doses of lamivudine with no
6 post-treatment follow-up incorporated into the study; the
7 interferon nonresponders study, which compared lamivudine
8 monotherapy for 52 or 68 weeks against placebo and an
9 active control combination lamivudine/interferon therapy
10 arm with a 16-week post-treatment period after the 52-week
11 treatment course; and the active control study, which
12 compared lamivudine against either interferon monotherapy
13 or combination therapy with no placebo control and had a
14 12-week post-treatment follow-up period.

15 The major emphasis of the FDA presentation will
16 be on selected aspects of the data for which additional
17 discussion may be useful. The analysis will focus on the
18 three placebo-controlled studies of lamivudine 100
19 milligrams per day and on the two principal, protocol-
20 predefined week 52 endpoints, histologic response defined
21 as an improvement of at least 2 points on the Knodell score
22 and e antigen seroconversion, a three-component composite
23 endpoint defined as loss of hepatitis B e antigen, gain of
24 e antibody, and fall in HBV DNA to below the limit of the
25 research solution hybridization assay employed in these

1 studies.

2 We will compare the week 52 end-of-treatment
3 results against off-treatment, end-of-follow-up results and
4 discuss the impact of missing values on the analysis.

5 There will be a brief discussion of results
6 from the interferon and combination therapy comparisons.

7 The three components of the composite
8 seroconversion endpoint will be examined briefly, with
9 additional exploratory analyses of the HBV DNA component of
10 this endpoint.

11 We will also summarize some exploratory
12 analyses of the occurrence treatment-emergent viral mutants
13 and outcomes that may be associated with these mutants.

14 We will begin by presenting the FDA efficacy
15 analysis, followed by a summary of key efficacy points,
16 then a presentation of safety data and a summary of key
17 safety points, and finally a brief listing of some
18 unresolved issues which arise in review of these data and
19 warrant further discussion.

20 Dr. Greg Soon will now present the FDA efficacy
21 analysis.

22 DR. SOON: Thanks, Dr. Styrt.

23 I'm Greg Soon, statistical reviewer for this
24 NDA.

25 This is an overview of my talk. First, I will

1 summarize the efficacy results for the histologic outcome
2 and the seroconversion status for lamivudine and placebo
3 treated subjects at week 52. Further, I will discuss the
4 relationship of these two measures. Then I will discuss
5 how treatment effects change from end of treatment to end
6 of follow-up. Finally, I will show the proportion of
7 subjects who met the seroconversion criteria at each visit,
8 as well as the components of this composite endpoint with
9 special emphasis on HBV DNA.

10 Now, I will first briefly review the efficacy
11 results for histologic improvement at week 52. Subjects
12 with a missing baseline Knodell score have been excluded.

13 This table shows the histologic improvement
14 rates for the three placebo-controlled studies which
15 includes the U.S. study, NUCA3010; the interferon
16 nonresponder study, which is NUCB3011; and the Asian study,
17 which is NUCB3009. The rows of this table contain the
18 histologic outcome. "Yes" means the subjects had a 2 or
19 more point improvement in total Knodell score, and "no"
20 means that they did not have such improvement. Missing
21 means the week 52 Knodell score was not available.

22 The numbers presented in the body of the table
23 are the percentages of subjects in each treatment arm with
24 various histologic responses. For example, in the U.S.
25 study for the lamivudine arm, histologic improvement

1 occurred in 55 percent of the subjects, and 27 percent did
2 not have such improvement. 18 percent were missing.

3 This can be contrasted with the placebo arm for
4 the U.S. study in which 25 percent had histologic
5 improvement. The test of difference of percent improved is
6 statistically significant. The comparison for the other
7 two studies are virtually identical.

8 Note that a minimum of 8 percent to a maximum
9 of 20 percent of the histologic evaluations are missing and
10 have been treated as failures. Even in the presence of
11 this amount of missing data, it is clear that the
12 lamivudine group has a better response rate than placebo.

13 Next we turn to the seroconversion.

14 Seroconversion is defined as loss of e antigen, gain of e
15 antibody, and HBV DNA below assay limit. A subject has
16 seroconversion status at a visit only if a subject met all
17 the three criteria at that visit.

18 We have chosen not to impute for missing e
19 antigen and e antibody using techniques such as last
20 observation carried forward. In our review of the data, we
21 were somewhat surprised that the e antigen and the e
22 antibody were not predictably durable. In these studies,
23 for subjects, whoever had a negative e antigen, 37 percent
24 had at least one positive value later. For subjects,
25 whoever had a positive e antibody, 39 percent had at least

1 one subsequent negative value.

2 In our primary analysis, the missing values
3 have been treated as a separate category in our tables
4 which implicitly treats missing observations as failures.
5 This is consistent with the approach we have adopted for
6 presentation to this committee.

7 This table displays week 52 seroconversion
8 status. The sample size you see here will be slightly
9 different than the previous slide on histology because this
10 analysis is restricted to subjects who had a positive e
11 antigen and a positive HBV DNA at baseline.

12 The first row shows the percent of subjects who
13 met all the seroconversion criteria at week 52 for each
14 treatment arm in the study. For the U.S. study, the
15 lamivudine rate is 17 percent versus 6 percent for placebo.
16 This comparison just passes the .05 level of significance,
17 but obviously this statistical evaluation is highly
18 dependent on how the missing data are treated in the
19 analysis.

20 For the interferon nonresponder study, the
21 response rates were nearly identical for the lamivudine
22 treated and the placebo treated subjects.

23 The Asian study showed a significant difference
24 and the amount of missing data is much lower.

25 Overall, we see much less statistical

1 consistency than was seen for histology. One study is
2 sensitive to the missing data. One was clearly negative
3 and the one was clearly positive.

4 On the next two tables, I will show the
5 relationship between seroconversion status and the
6 histologic outcome. These analyses were conducted to see
7 if the seroconversion endpoint is a reliable indicator of
8 the biopsy outcome.

9 This slide shows the lamivudine treated
10 subjects in the U.S. study. My next slide will show the
11 results for the placebo arm. This is a cross tabulation of
12 seroconversion status by histologic improvement. The table
13 shows number of subjects instead of percent of subjects.

14 If you look at the upper left corner of the
15 table, you can see that most of the subjects who have
16 seroconversion status equal to yes at week 52 also had
17 histologic improvement. That's 9 versus 1.

18 On the other hand, for those who did not meet
19 the three seroconversion criteria at week 52, 21 showed
20 histologic improvement while 16 did not.

21 Other studies showed similar results which
22 suggests that the ability of seroconversion status to
23 indicate the histologic outcome is limited.

24 These are the results for the placebo arm. We
25 can see that there are too few seroconverters to permit a

1 comparison with the results for lamivudine.

2 Now we turn to the second part of my talk which
3 will compare the end of treatment at week 52 with the end
4 of follow-up at week 68. Because we have no histologic
5 evaluation at week 68, this analysis uses the
6 seroconversion status only.

7 This table presents the number of subjects for
8 the lamivudine group in the U.S. study. The placebo group
9 will be shown on the next slide. Recall that treatment was
10 discontinued at week 52.

11 Of the subjects who met the three
12 seroconversion criteria at week 52, 8 also met the criteria
13 at week 68 and 3 no longer met the criteria.

14 Of the subjects who did not meet the three
15 criteria at week 52, 3 met the criteria at week 68 and 38
16 did not.

17 It is interesting to note that exactly the same
18 number of subjects meet the criteria both week 52 and week
19 68, but this is because the gains and the losses are in
20 exact balance.

21 For placebo treated subjects, no subjects lost
22 the seroconversion status and 2 subjects gained status from
23 week 52 to week 68. However, a few placebo treated
24 subjects lost the seroconversion status in the only other
25 placebo-controlled study with the follow-up data. There

1 | were really too few subjects to comment on the durability
2 | of seroconversion status for placebo subjects.

3 | Comparison of lamivudine and placebo at week 52
4 | and week 68 will be presented later graphically, as well as
5 | all other time points measured. These tables have shown
6 | that the proportions over time reflect the gains and the
7 | losses.

8 | In the remainder of my presentation, I will
9 | show how the seroconversion status and its components
10 | change over the course of the trial.

11 | This is an exploratory analysis using subjects
12 | with complete data at a given time point. This differs
13 | from the primary analysis in which missing data were listed
14 | separately. We have done this to avoid having the graphs
15 | decrease over time due to an increasing amount of missing
16 | data. However, the graphs with missing values, included as
17 | failures, showed the same patterns. We have analyzed the
18 | subjects based on their randomized treatment assignment.
19 | We have also only included subjects with detectable
20 | baseline e antigen and HBV DNA.

21 | This is the U.S. study. In this graph and
22 | future graphs, a solid line represents active treatment and
23 | the dashed line represents either placebo or no treatment.
24 | The white dashed line represents the placebo arm. The
25 | orange is lamivudine 100 milligrams. Note that the orange

1 line changes from solid to dashed at week 52, showing that
2 these subjects received no treatment at week 52.

3 This is the proportion of subjects who met all
4 three seroconversion criteria. This is shown for each time
5 point. The sample size decreases over time due to
6 dropouts. For example, 16 percent were missing at week 52
7 for post-treatment arms. From the plot, we can see that
8 over the course of the study, the proportion of subjects
9 who met all three seroconversion criteria increased in both
10 the lamivudine and placebo groups. Recall that the
11 statistical comparison at week 52 was not robust. In fact,
12 the difference varies before and after week 52. This
13 reflects changes brought about by a small number of
14 subjects.

15 This is the first in a series of three slides
16 for the interferon nonresponder study. This slide compares
17 the two lamivudine arms to investigate the question of
18 continued therapy versus 52 weeks of therapy. We will see
19 that this study does not provide convincing evidence that
20 therapy beyond 1 year provides additional benefits.

21 The next two slides will compare the lamivudine
22 arms to placebo and then with the combination of lamivudine
23 and interferon.

24 Subjects in the two arms shown here received
25 identical treatment through week 52. The group shown in

1 yellow was assigned to receive lamivudine through week 68.
2 The orange line represents subjects assigned to receive
3 lamivudine for 52 weeks followed by placebo.

4 It can be seen that these two treatment groups
5 diverge before discontinuation of treatment. Since these
6 subjects had received identical treatment before week 52,
7 the divergence is simply due to chance, and the difference
8 at week 68 maybe are not effects of the preexisting
9 difference at week 52. As such this study may not provide
10 conclusive support for longer-term treatment.

11 Now let's add the placebo arm to this graph.
12 Placebo is the white line. Again, the seroconversion rate
13 goes up during the course of study. You can see that the
14 two lamivudine arms are not clearly separated from the
15 placebo arm.

16 Now let's add the interferon and the lamivudine
17 combination arm. The green line represents the combination
18 arm with active treatment discontinued at week 24. These
19 subjects received lamivudine in the first 24 weeks and
20 interferon from week 8 to week 24. It is clear that the
21 combination arm is numerically but not significantly worse
22 than placebo at week 52.

23 In summary, this trial does not allow us to
24 distinguish between lamivudine and placebo between 52 and
25 68 weeks of lamivudine, nor the contribution of combination

1 therapy with respect to seroconversion.

2 This is the active control study. Orange
3 represents lamivudine, blue is interferon monotherapy, and
4 the green is combination therapy.

5 At week 52 the combination arm is numerically
6 superior to the two monotherapy arms, but this did not
7 achieve statistical significance after adjusting for
8 multiple comparisons. Note also that the week 52 results
9 appear somewhat atypical of the pattern seen over the
10 course of the trial. The two monotherapies, represented by
11 orange and blue, had similar response rates. With sample
12 sizes of 64 and 80 subjects, the resulting confidence
13 interval for the difference of response rates between the
14 two monotherapies at week 52 had upper and lower bounds
15 nearly as great as the response rates, suggesting that we
16 do not have enough data to rule out a difference favoring
17 either treatment.

18 The other placebo-controlled study is the Asian
19 study. Three points are shown here because e antibody was
20 available only for weeks 24 and 52. Again, the orange line
21 is lamivudine 100 milligram and the white is placebo. The
22 pink line with hollow circles is lamivudine 25 milligram.
23 Similar to what we have seen in the previous slides, the
24 proportion of subjects meeting the seroconversion criteria
25 at each visit increased over time for all three arms. By

1 week 52, there is a difference in the proportion of
2 subjects meeting seroconversion criteria between lamivudine
3 100 milligrams and placebo, and it is statistically
4 significant, as we mentioned at the beginning of the talk,
5 but no difference was established between the two
6 lamivudine doses.

7 Now, we will change gears a little bit and
8 examine how seroconversion is driven by its component
9 measures, which include e antigen, e antibody, and HBV DNA.

10 These are the results for the U.S. study. The
11 bottom white line represents the composite endpoint. This
12 is the proportion of subjects who met all three criteria at
13 each time point. The orange line represents the proportion
14 of subjects who were e antigen negative. The green is the
15 proportion with e antibody positive, the yellow is the
16 proportion of HBV DNA below assay limit.

17 From the plot, we see that among the three
18 components, e antigen and e antibody are very similar to
19 the composite, but the HBV DNA component is different.
20 While seroconversion rates and the rates of e antigen
21 negative and e antibody positive increase over the course
22 of the trial, the proportion of subjects with HBV DNA below
23 assay limit increased initially and then seemed to decrease
24 even during the active treatment.

25 For this reason, we will single out the HBV DNA

1 component for further analyses. These analyses will be
2 presented in the following slides.

3 This is the U.S. study. Orange is lamivudine
4 and the white is placebo. The lamivudine line was shown on
5 a previous slide. As I mentioned previously, there was an
6 initial rapid rise in the proportion of subjects with HBV
7 DNA below assay limit. After that, there is a continual
8 decrease, and this decrease began well before the end of
9 active treatment.

10 In the placebo group, the proportion of HBV DNA
11 below assay limit rises gradually over time. This graph
12 raises the possibility that there may be a loss of relative
13 efficacy well before the discontinuation of treatment.

14 This is the interferon nonresponder study.
15 Yellow is lamivudine for 68 weeks. Orange is lamivudine
16 for 52 weeks, and the white is placebo. Again, the
17 lamivudine arms peak at week 24 or before that and then
18 decline steadily. This relationship is consistent with the
19 findings in the U.S. study.

20 Now, let's add the interferon and the
21 lamivudine combination arm. The green line represents
22 combination therapy. For this treatment, the proportion of
23 HBV DNA below assay limit increases while on treatment, but
24 once the active treatment is stopped, the proportion
25 declines rapidly and it then follows the path of the

1 placebo arm.

2 This is the active control study. Lamivudine
3 is shown in orange, interferon monotherapy in blue, and the
4 combination therapy in green. The patterns we see here for
5 the lamivudine monotherapy and the combination therapy are
6 similar to the other studies; that is, for the lamivudine
7 group, the proportion of HBV DNA below assay limit peaks
8 before week 24 and then declines even when the subjects
9 were on active treatment, while for the combination arm,
10 the response rate rises during treatment but drops off
11 rapidly after stopping the active treatment.

12 Subjects in interferon monotherapy received
13 placebo for 8 weeks, followed by 16 weeks of placebo and
14 interferon therapy, and are then followed by no treatment.
15 The response rate increased between weeks 8 and 24 during
16 active treatment, then stays relatively stable after
17 discontinuation of treatment.

18 The last study is the Asian study. This study
19 appears to be different from the other studies. Again, the
20 orange is lamivudine and the white is placebo. The
21 additional pink line with hollow circles is lamivudine 25
22 milligram. Contrary to the patterns we have seen earlier,
23 the proportion of HBV DNA below assay limit does not
24 decline after its initial rise. Rather, the proportion of
25 HBV DNA below assay limit for both the 100 milligram dose

1 and the 25 milligram dose peak around week 8 with no
2 apparent subsequent decline.

3 The placebo group is similar in pattern to the
4 other studies.

5 Now I'll return the podium to Dr. Styrt.

6 DR. STYRT: I'd like to recapitulate a few of
7 the points from Dr. Soon's presentation that may be
8 important in the consideration of this NDA.

9 The end-of-treatment histologic response to 52
10 weeks of lamivudine was superior to placebo in all three
11 placebo-controlled studies with a significant treatment
12 effect that was consistent across studies.

13 Results of the principal seroconversion
14 comparison varied in the different studies and over time
15 within studies. There was one study, the Asian study, with
16 a statistically significant difference between lamivudine
17 and placebo groups, one study, the interferon nonresponder
18 study, with no apparent difference between lamivudine and
19 placebo in the principal predefined seroconversion
20 endpoint, and one study, the U.S. study, in which
21 statistical significance was sensitive to the treatment of
22 missing values, but overall results appeared similar to the
23 Asian study.

24 We were fortunate in having three placebo-
25 controlled studies with consistent histologic results, as

1 it would have been far more difficult to draw conclusions
2 from the seroconversion data alone or from the active
3 control data.

4 The comparison of end-of-follow-up against end-
5 of-treatment seroconversion status was inconclusive. It
6 was not possible to determine whether there was a reliably
7 persistent treatment effect after stopping therapy, but it
8 could not be demonstrated that there was no persistence.

9 In addition, subjects moved in and out of the
10 groups meeting the seroconversion criteria and each of its
11 component criteria during therapy and after therapy.

12 There were also some inconsistencies in
13 components of the predefined serologic endpoint. For
14 example, there was a marked treatment-related discrepancy,
15 as you have heard, between prospectively defined three-
16 component seroconversion and its e antigen component in one
17 of the studies, and this illustrates the potential need for
18 more study of the interrelationships between different
19 markers and endpoints used in hepatitis B studies.

20 Seroconversions did occur in placebo
21 recipients. The frequency of these responses was
22 consistent with reports of spontaneous e antigen
23 seroconversion in the literature, but was sufficiently
24 different in different studies to have an impact on the
25 interpretation of treatment effect for the active drug.

1 In the studies with interferon containing
2 comparator arms, no evident advantage was seen for
3 combination therapy. The active control study did not show
4 any substantial difference between lamivudine and
5 interferon monotherapies, but did not have the power to
6 rule out the possibility of clinically meaningful
7 differences in favor of either arm.

8 In addition, it was not possible from the
9 results of this study to confirm whether the timing of
10 treatment and of principal evaluations on treatment for
11 lamivudine monotherapy and after 6 months off-treatment for
12 interferon represents the most appropriate study design for
13 comparison of these therapies.

14 When we looked at subjects with HBV DNA below
15 the assay limit at each time point, a very high proportion
16 of lamivudine recipients in all studies achieved levels
17 below the assay limit early in therapy. However, this
18 striking early rise was followed by a decline in the
19 proportion of subjects with HBV DNA below the assay limit.
20 This decline began before the end of therapy, such that
21 about one-third of subjects with this early response were
22 again HBV DNA assay positive on therapy at week 52. It's
23 not clear whether this pattern could be better defined with
24 different assays given the many differences between the HBV
25 DNA assays in current use, but within the measurements

1 employed in these studies, there appeared to be a response
2 which was partially reversed during the treatment period.

3 It was very difficult to draw conclusions about
4 the optimal duration of lamivudine therapy, and many of the
5 points I've already mentioned contributed to this
6 difficulty. For example, the changes over time in placebo
7 recipients complicate any assessment of the value of
8 successive increments of treatment. The meaning of
9 different histologic assessment systems can be debated and
10 the number of time points examined histologically is
11 necessarily small. The number of seroconverters in these
12 studies was too small to permit conclusions about loss or
13 persistence of seroconversion-defined treatment effects
14 after stopping therapy. The number of seroconversions
15 during extended therapy was also too small for confident
16 interpretation.

17 You have seen the graphical representation of
18 the difference between 68-week and 52-week lamivudine
19 groups at week 68 in the interferon nonresponder study
20 which appeared very much like the difference between the
21 same groups at or before week 52 when their treatment was
22 identical.

23 We have also performed preliminary analyses of
24 data from study NUCB3018, the follow-on study from the
25 Asian study. Of the subjects in that study who received

1 lamivudine 100 milligrams per day for the first year and
2 were assigned to continue for a second year, we are not
3 able to identify a net increase in seroconversions of more
4 than a few percentage points in the second year and cannot
5 clearly differentiate this effect for what might occur
6 without treatment.

7 Whether during or after treatment, the
8 persistence of treatment-related changes in the components
9 of the seroconversion endpoint was less than might have
10 been expected, although early results from one of the
11 follow-on studies suggests that seroconversions or e
12 antigen loss lasting at least a few months may prove to be
13 more predictive of long-term persistence. A single
14 negative e antigen, positive e antibody, or even three-
15 component seroconversion at one time point did not
16 necessarily indicate that no reversion would occur.

17 For the HBV DNA component of the seroconversion
18 endpoint, the subgroup of subjects with a fall below the
19 assay limit followed by reemergence of DNA before the end
20 of treatment was large enough to raise concerns about
21 whether part of the study population is experiencing an
22 early response and then losing treatment effect despite
23 continuation of the drug.

24 Overall, the issues arising from the efficacy
25 analysis suggest that there are still challenges to be met

1 in defining the best predictor of either short-term or
2 long-term clinical benefit in chronic hepatitis B and
3 defining the best treatment regimens to produce this
4 benefit.

5 In the safety presentation, I'm going to start
6 by discussing some exploratory analyses of outcomes in
7 subjects who experienced reemergence of HBV DNA and/or
8 development of viral mutations during lamivudine therapy.
9 We considered these events to represent a combination of
10 safety and efficacy issues, as the risk/benefit
11 calculations for long-term therapy may be substantially
12 altered in any patient subgroups having diminished benefit
13 from treatment while remaining at risk for toxicity.

14 I will then outline some of the questions that
15 have arisen about exacerbations of liver dysfunction as
16 treatment-related events in studies of lamivudine and other
17 clinical and laboratory adverse events in the clinical
18 trials.

19 Finally, I will mention some potential concerns
20 with use of the drug in special populations which again may
21 be considered as combined safety/efficacy issues.

22 Starting with HBV DNA reappearance during
23 therapy, we wanted to see what the available data could
24 tell us about the disease status of subjects who apparently
25 responded to treatment and then became DNA positive again.

1 For this purpose, we performed exploratory analyses of
2 subjects in all four studies who received lamivudine 100
3 milligrams per day for at least 52 weeks and had at least
4 one HBV DNA below the assay limit for the solution
5 hybridization assay before week 24, which we will call
6 early suppression.

7 We divided these subjects into two groups
8 defined as follows. Subjects with reappearance of HBV DNA
9 on therapy experienced early suppression, but were HBV DNA
10 positive again at week 52. Persistently suppressed
11 subjects experienced early suppression and were also below
12 the assay limit at week 52. We used the combined results
13 from all placebo subjects as an additional comparator.

14 This slide shows a brief summary of the
15 analyses of week 52 endpoints for these groups. The
16 numbers are tabulated in your background package. Subjects
17 with HBV DNA reappearance on therapy had a higher
18 proportion of histologic responders than placebo subjects
19 but some of them may have been exposed to recrudescent
20 virus for only a short time.

21 Subjects with HBV DNA reappearance on therapy
22 appeared to have a magnitude of change in the Knodell score
23 intermediate between persistently suppressed subjects and
24 placebo subjects.

25 Subjects with HBV DNA reappearance were less

1 likely to have negative e antigen, positive e antibody, or
2 normal ALT at week 52 than persistently suppressed subjects
3 and looked rather more like the placebo recipients for
4 these endpoints.

5 HBV DNA reappearance on therapy was more common
6 in subjects with viral mutations which have been associated
7 with reduced viral susceptibility to lamivudine. However,
8 this correspondence was not absolute as there were also
9 some subjects with HBV DNA reappearance who did not have
10 these mutations detected and some persistently suppressed
11 subjects who did have such mutations. It was possible to
12 define genotypes for many of the persistently suppressed
13 subjects as mutations were sought using a PCR based assay
14 while HBV DNA suppression was defined here by the solution
15 hybridization assay.

16 We also looked more closely at groups of
17 subjects defined by analyses of viral genotype at week 52.
18 Mutations in the YMDD region of the viral genome associated
19 with reduced in vitro lamivudine susceptibility have been
20 seen, as you have heard, in some subjects with viral
21 breakthrough during lamivudine therapy, and PCR based
22 assays for these mutations were performed for a substantial
23 proportion of the subjects in the four principal phase III
24 trials at 52 weeks and for smaller numbers of subjects at
25 selected earlier time points.

1 YMDD mutations were not seen in specimens from
2 placebo subjects in these trials, were infrequent at 24
3 weeks of lamivudine therapy, and increased in frequency
4 between weeks 24 and 52, and again between week 52 and week
5 104 in the limited data from NUCB3018.

6 When YMDD mutations were detected, specimens
7 might be reported as either mixed or fully mutant, and
8 these categories will be combined when we refer to any
9 mutant in the following table.

10 This table shows the occurrence of YMDD
11 mutations by 52 weeks for subjects receiving lamivudine 100
12 milligrams per day in each of the four principal phase III
13 trials expressed as a percentage of all specimens that were
14 reported with a genotype result or a result of no PCR
15 amplifiable DNA. The bottom row of the table shows the
16 percentage of mutant containing specimens that were
17 reported as fully mutant.

18 Note that three of the studies, the U.S. study,
19 the interferon nonresponders study, and the active control
20 study, had about 30 percent of specimens reported as
21 containing mutants, ranging from 27 to 32 percent, and in
22 each of these studies, most of the mutant-containing
23 specimens were reported as fully mutant.

24 On the other hand, the Asian study had a much
25 lower prevalence of mutations at 1 year of treatment, 16

1 percent, or not much more than half of what was seen in the
2 other studies. Furthermore, only one-third of the mutant-
3 containing specimens in this study were reported as fully
4 mutant. You'll recall that this was the study which did
5 not show a progressive decline in proportion of subjects
6 with HBV DNA below the assay limit during treatment.

7 However, in the subset of these subjects who
8 were assigned to continue 100 milligrams of lamivudine for
9 a second year in study NUCB3018 and had repeat genotype
10 determinations at week 104, mutants were detected in 42
11 percent of week 104 specimens with results available and
12 most of those were reported as fully mutant.

13 This slide shows brief conclusions from the
14 exploratory analysis of outcomes according to genotype at
15 the end of a year of therapy. Again, the numbers are in
16 your background package and the results are similar to
17 those for subjects with HBV DNA reemergence, some but not
18 all of whom are the same subjects.

19 Subjects with fully mutant virus had a higher
20 proportion of histologic responders than placebo subjects,
21 but knowing that most of these viral mutations appear to
22 emerge late in the year of therapy, we don't know how long
23 the liver had been exposed to them at the time of biopsy.

24 Subjects with fully mutant virus tended to have
25 magnitude of Knodell score changes intermediate between

1 placebo recipients and lamivudine subjects with non-mutant
2 virus.

3 They were less likely to have negative e
4 antigen, positive e antibody, HBV DNA below the solution
5 hybridization assay limit or normal ALT at 1 year than
6 lamivudine treated subjects with wild-type virus and
7 appeared more similar to placebo subjects on these
8 outcomes. All subject categories, including placebo
9 subjects, tended to have HBV DNA and ALT at 1 year that
10 were below their individual baselines.

11 Subjects with mixed viral populations were few
12 in number and results were somewhat erratic, but generally
13 they showed results intermediate between lamivudine
14 recipients with wild-type virus and subjects with fully
15 mutant virus.

16 What happens if treatment is stopped in the
17 presence of viral mutants? There were even smaller numbers
18 of subjects to look at here. And these are not so much
19 conclusions as suggestions that more information may be
20 needed.

21 Subjects with fully mutant virus did not have
22 much change in ALT and HBV DNA levels after stopping
23 treatment. They looked much like the placebo subjects and
24 had less suggestion of rebound than lamivudine treated
25 subjects with wild-type virus.

1 Subjects with mixed mutants did have post-
2 treatment rises in ALT and HBV DNA, but the magnitude was
3 difficult to compare with other groups due to the small
4 number of subjects.

5 In the very few subjects with mixed or fully
6 mutant virus at 1 year and repeat genotypes available after
7 4 months off therapy, reemergence of wild-type was detected
8 in most but not all, and most of these still had some
9 detectable mutants often as mixed genotypes. About one-
10 quarter of the subjects with fully mutant genotypes at week
11 52 were also reported fully mutant at week 68 in the data
12 available from the time points.

13 Results from the subjects with HBV DNA
14 reappearance and/or reemergence of YMDD mutations on
15 therapy raised some questions about whether there may be
16 patient groups who have diminished treatment benefit over
17 time. We could not be absolutely sure that these subjects
18 were better off at week 52 than if they had received
19 placebo for a year and were much less able to draw
20 conclusions about whether they were better off continuing
21 lamivudine than if they had stopped at the time of HBV DNA
22 reemergence or detection of mutations.

23 More information is needed to define the risks
24 and benefits of treatment continuation in such patients.
25 Ideally it would be desirable to be able to define groups

1 of patients who would benefit from very long-term therapy,
2 patients who have achieved definitive benefit, for example,
3 whether most subjects with short-term durable
4 seroconversion will show clinical stability off treatment
5 over the long term, and patients who should consider
6 stopping treatment because they may no longer be benefiting
7 but remain at risk for adverse events if treatment is
8 continued. And from the data so far, there may be a need
9 to demonstrate whether some patients with HBV DNA
10 reemergence or YMDD mutations fall into such a category.

11 Moving on to some of the hepatic adverse events
12 that have been reported in lamivudine clinical trials. In
13 the controlled trials with post-treatment follow-up, a
14 substantial minority of subjects had transaminase flares
15 after stopping lamivudine, which have been described to you
16 by the applicant. Most such flares reportedly did not lead
17 to clinical problems, and there is insufficient information
18 to predict the results if patients are retreated.

19 In open-label studies that often enrolled much
20 sicker patients, there have been occasional reports of
21 clinically significant hepatic decompensation reported by
22 the investigators to be potentially related to drug
23 withdrawal, including a few with fatal outcomes.

24 Hepatitis flares associated with seroconversion
25 have previously been reported in patients with chronic

1 hepatitis B, and in active control study NUCB3010, the
2 applicant's analysis reports four cases in which liver
3 function test elevations were reported as serious adverse
4 events and were associated with seroconversion in the
5 lamivudine arm.

6 We previously noted that subjects with YMDD
7 mutations tended to have week 52 ALTs than lamivudine
8 treated subjects with wild-type virus. In the various
9 study reports so far, we have seen four reports of deaths
10 in subjects with YMDD mutant virus. Two of those were in
11 patients who received lamivudine as immunocompromised
12 transplant recipients in compassionate use settings. The
13 others in two other studies outside of the four principal
14 phase III trials.

15 In all of these reports, the ability to
16 interpret causality is limited by the fact that we're
17 seeing deterioration of liver function that could be
18 related to the patient's underlying disease and there is
19 not adequate information to delineate the extent to which
20 lamivudine use or cessation could contribute to such
21 outcomes.

22 As you're probably all well aware, lamivudine
23 has had extensive use in the treatment of HIV infected
24 patients, and the current label carries warnings or
25 precautions concerning the possibilities of lactic acidosis

1 and hepatic steatosis, pancreatitis, and post-treatment
2 hepatitis flares. Laboratory values from clinical trials
3 in HIV described in the label show modest increases in
4 reports of neutropenia, liver function test, and amylase
5 elevations in lamivudine-containing treatment arms.
6 However, the clinical adverse event profile has not shown
7 major differences between placebo and lamivudine recipients
8 in most of these HIV treatment studies.

9 In the four principal phase III trials in
10 chronic hepatitis B, lamivudine subjects had more grade 3
11 and 4 elevations in CPK and lipase than placebo subjects in
12 each study for which this comparison could be made. That
13 is, each of the three placebo-controlled studies had some
14 increase in grade 3 and 4 CPK elevations and the two
15 placebo-controlled studies that measured lipase had an
16 increase from 7 percent in the placebo arm to 10 percent in
17 the lamivudine arm in lipase values greater than 2.5 times
18 the upper limit of normal.

19 The clinical significance of these laboratory
20 variations is unclear and the subjects have not been
21 reported as having major clinical manifestations. But
22 these laboratory values may signal a need to be alert for
23 possible muscle or pancreatic events with more widespread
24 use of the drug in more heterogeneous populations.

25 The adverse events profiles in these trials

1 have also been presented to you in greater detail by the
2 applicant, and no common new adverse events have been
3 evident in hepatitis trials relative to experience with
4 lamivudine in HIV therapy.

5 In the trials with interferon treatment arms,
6 adverse events appeared compatible with those previously
7 identified in trials of interferon.

8 There are several special populations in which
9 more information may be needed about lamivudine for chronic
10 hepatitis B. In patients with decompensated liver disease,
11 it's very difficult to derive information about drug-
12 specific events when the underlying risk of adverse events
13 is high, but there is no suitable comparator to determine
14 which events could be associated with therapy.

15 In HIV/HBV dually infected patients, there is
16 very limited adverse event information from retrospective
17 analysis of subjects in HIV trials who had serologic
18 evidence of concurrent hepatitis B virus infection, and
19 some excessive neutropenia has been reported in lamivudine-
20 containing treatment arms, as well as shifts to ALT levels
21 higher than the subject's baseline.

22 There is also the potential concern of whether
23 some dually infected subjects might be started on
24 lamivudine for chronic hepatitis B and inadvertently have
25 drug-resistant HIV selected out.

1 In children there is very little information on
2 lamivudine in chronic hepatitis B with a safety database of
3 about 50 subjects treated for 4 weeks at varying doses, HBV
4 DNA measurements using a different assay from the principal
5 adult studies, and no opportunity to derive information on
6 the relative potential for completeness and rapidity of
7 viral suppression, seroconversion or histologic outcomes,
8 emergence of viral mutations, or long-term toxicity.

9 To summarize the major safety points that have
10 arisen in consideration of these data, the reemergence of
11 HBV DNA and/or emergence of YMDD mutations appear to have
12 potential associations in these exploratory analyses with
13 outcomes suggesting diminished treatment benefit. The
14 potential for exacerbations of liver dysfunction, either
15 during therapy or in association with stopping therapy, is
16 a concern, and more information would be desirable on the
17 risks in different patient groups.

18 In summary, we have three different studies in
19 support of the safety and efficacy of lamivudine for
20 chronic hepatitis B with a very consistent effect on the
21 primary histologic outcome and more variable indicators of
22 beneficial effect on seroconversion outcomes. As a
23 preliminary to further discussions, we'll note that the
24 information in this NDA raises some interesting and
25 unresolved issues.

1 For evaluating efficacy, designing future
2 trials, and monitoring individual patients, it would be
3 desirable to have more definitive information about the
4 best markers for predicting short or long-term benefit in
5 chronic hepatitis B. How frequently changes over time in
6 this disease are due to drug therapy as compared to events
7 that would occur spontaneously and how durable the drug-
8 induced changes will be either on or off therapy remains a
9 challenge to determine even in controlled trial settings.

10 While uncontrolled data are even more difficult
11 to interpret, at this stage of development, it's often
12 unclear what is the best comparison group for evaluating a
13 new treatment and the best trial design for making these
14 comparisons. A major issue in future trial design may be
15 how best to evaluate the potential for combination
16 therapies.

17 Among the unresolved safety issues, more
18 information on patterns of liver dysfunction and hepatitis
19 flares associated with either use or cessation of
20 lamivudine would be of particular interest and information
21 on the effect of retreatment in patients who have rebound
22 or relapse after stopping drug could be important to many
23 treatment decisions.

24 In addition, very long-term effects of this
25 drug in chronic hepatitis B are, of course, yet unknown.

1 | There are several potential patient populations for whom
2 | more information could result in altered assessments of the
3 | risk/benefit balance of various treatment strategies.
4 | These include patients with decompensated liver disease,
5 | pediatric patients for whom safety and efficacy have not
6 | been demonstrated, and treated patients who seroconvert --
7 | should they stop therapy while they have a durable response
8 | -- or who develop viral reemergence and/or resistance
9 | related mutations. Can we predict who is most at risk for
10 | such events, and should some of these patients stop therapy
11 | because its benefit is diminishing or lost?

12 | Overall, the studies presented here show some
13 | encouraging results but also illustrate how much more it
14 | would be useful to know about selection of treatments,
15 | selection of patients for treatment, timing and duration of
16 | lamivudine therapy for hepatitis B.

17 | Thank you.

18 | DR. HAMMER: Thank you very much.

19 | I'm going to ask that we defer questions for
20 | the FDA presentation until after lunch and move to the open
21 | public hearing because some of the individuals who have
22 | signed up have afternoon commitments. So, we will move to
23 | the open public hearing. I would ask that the people who
24 | come to the microphone, identify themselves, speak for no
25 | more than 4 to 5 minutes, and announce any financial

1 disclosures that are relevant.

2 The first individual is Scott Lincoln.

3 MR. LINCOLN: As the Chairman said, my name is
4 Scott Lincoln, and I would like to inform the committee
5 that the expense to fly me here to Washington from San
6 Francisco has been covered by Glaxo Wellcome.

7 I would also like to say thank you to the
8 committee for allowing me to speak about my health
9 experience and how my health has improved since I started
10 taking the drug lamivudine.

11 I also wanted to put a face and a name to
12 hepatitis B.

13 I was diagnosed with hepatitis B in December of
14 1991 at the age of 28. I became quite ill from the start.
15 Within a month, I began to experience excruciating pain in
16 my legs. As the months progressed, my health continued to
17 decline. By May of 1992, I was taking 30 milligrams of
18 valium because the pain had increased so in my legs. The
19 pain was so intense that I slept about a couple of hours
20 each day. Suicide seemed to be my only escape from pain,
21 and I came very close to ending my life.

22 By June I was begging my doctor to see a
23 neurologist. After seeing the neurologist and having two
24 biopsies taken from my calves, consisting of nerve,
25 vessels, tissue, I was diagnosed with polyarteritis nodosa,

1 a vascular disease brought on by the hepatitis B. The
2 sedimentation of my blood was at 153 when normal is 13.
3 The polyarteritis nodosa, PAN for short, was ravaging my
4 organs and my joints.

5 August and September of 1992, my health
6 continued to decline. I was on massive doses of steroids
7 and spent many hours in the emergency room due to
8 uncontrollable vomiting.

9 By the middle of September, my doctors had
10 realized that the PAN had killed my gallbladder and I had
11 emergency surgery to remove it. My parents arrived from
12 the Midwest while I was still in surgery.

13 6 days later my bowel perforated which caused
14 peritonitis. Once again, surgery was performed and my
15 bowel was repaired. Other complications had arisen and my
16 condition was serious by this time.

17 I was then given my first dose of Cytoxan, a
18 chemotherapy drug, to suppress my immune system since it
19 was trying to kill me. 10 days later my bowel perforated
20 three more times.

21 My mother was told to call the rest of the
22 family since they did not expect me to live. This time
23 they removed a little over a foot of my bowel. I never
24 thought I would leave the hospital alive.

25 The next 3 weeks I was given more Cytoxan and

1 was still taking high doses of steroids. Finally, this
2 treatment seemed to be working. My prognosis was not good,
3 but my faith and determination were strong. I was released
4 from the hospital on November 8th, 1992 and was being cared
5 for at home by my mother. I weighed 98 pounds and no
6 longer could walk.

7 I continued to receive monthly injections of
8 Cytosan for 1 year. The treatment made me very ill and
9 there were many times I wondered if it was worth it all. I
10 had lost my career. I had to file bankruptcy, and I now
11 lived on Social Security. I was still determined to
12 survive and I started walking with assistance and continued
13 to improve slowly as the years went by.

14 By October of 1995, I was experiencing severe
15 pains in my right side. This is when it was determined
16 that the hepatitis B was now chronic and my liver was
17 failing. By January of 1996, the hepatitis B was
18 replicating so fast that my case was transferred to the
19 University of California at San Francisco to be placed on
20 the liver transplant list. I was in the end stages of
21 liver disease.

22 At the same time, I had been screened and
23 approved to enter a study with a drug called lamivudine.
24 On February 6th, 1996, I started taking 100 milligrams of
25 lamivudine. Within 2 weeks I had started to notice an

1 improvement in my health, and those improvements were I
2 wasn't confused. I could eat. The fatigue was
3 considerably less. By the end of the first year on
4 lamivudine, my liver enzymes were back to normal and my
5 health had dramatically improved. After 6 years, I
6 reentered the work force in August of 1997.

7 Being here today and knowing this drug can save
8 lives gives meaning to the hell that I went through.
9 Please approve lamivudine for the use with hepatitis B so
10 no one else will have to suffer as I have.

11 Thank you.

12 DR. HAMMER: Thank you very much.

13 The next speaker is Timothy Block.

14 DR. BLOCK: I'm Timothy Block. I'm a professor
15 from Jefferson Medical School and the cofounder of the
16 Hepatitis B Foundation and a member of the Delaware Valley
17 Chapter of the American Liver Foundation.

18 I'd also like to thank the committee for
19 allowing me to speak. I disclose that Glaxo Wellcome has
20 made contributions to the Hepatitis B Foundation and has
21 offered to pay for my travel here.

22 The Hepatitis B Foundation is a nonprofit
23 organization that's dedicated to finding a cure for
24 hepatitis B, promoting awareness about the problem of
25 hepatitis B. When we founded the Hepatitis B Foundation in

1 1991, it was because of a personal story of a small boy who
2 was infected with hepatitis B, and at that time there were
3 no therapeutic options. That child, like hundreds of
4 millions of other children like him, faced a lifelong
5 stigma and life with a time bomb inside him of a virus that
6 could go off and cause consequences because, of course,
7 nobody knows which of the 300 million hepatitis B carriers
8 in the world will ultimately suffer the severe symptoms
9 associated with the virus infection.

10 At that time we were assured by our clinicians
11 and by others that with proper attention and resources,
12 good therapies for the treatment of this disease were right
13 around the corner. I decided to change my professional
14 career and work towards promoting awareness about hepatitis
15 B and studying it for myself.

16 As I mentioned, what I'd like to do now in the
17 next couple of minutes is tell you again and put the
18 personal faces, as the gentleman before me did, on the 300
19 million individuals who are chronically infected and face
20 lifelong doubt.

21 Despite the availability of a safe vaccine,
22 which is of course of no value to those who are already
23 infected, there still remain more than 200,000 infections
24 in this country alone annually with hepatitis B. Most of
25 those are in the young adult population.

1 I'd like to say now that we're very optimistic
2 about the future for those who are infected with hepatitis
3 B because perhaps the predictions of the experts who
4 counseled us 8 years ago may be coming true.

5 Of course, interferon alfa is the only
6 currently approved therapy for hepatitis B, and its even
7 limited therapeutic value gives us hope that this is a
8 disease that can be cured. But interferon alfa is only
9 valuable in a minority of the population of those infected
10 with hepatitis B, and for anyone who has been involved as a
11 caregiver or as a counselor or as an infected individual,
12 the untoward side effects of interferon make it imperative
13 that alternatives be found.

14 We believe, because we're aware of the animal
15 data, of the human data that are coming, that perhaps
16 lamivudine is our current best hope. It's of course just
17 the most developmentally advanced in a whole series of so-
18 called polymerase inhibitors. Hopefully it won't be the
19 last of these drugs that you'll be seeing, but it's
20 certainly the one that we're facing as giving us the most
21 hope right now.

22 It's worth mentioning that the oral
23 availability and low toxicity, relative well tolerance
24 makes it all the more attractive and user friendly.

25 Of course, we'll be keeping an eye on the

1 ultimate efficacy of the drug and mindful of the resistant
2 mutants that emerge and other possible drug interactions.
3 But nevertheless, it's the medication that's giving us the
4 most hope.

5 So, I hope from the human side that other
6 effective therapies will be found and you'll be considering
7 those soon. But right now lamivudine gives us the current
8 best hope.

9 Thank you very much.

10 DR. HAMMER: Thank you.

11 Nelson Whittington?

12 MR. WHITTINGTON: Good afternoon. I would like
13 to say welcome to the committee and to guests. I am from
14 Fort Lauderdale. My name is Nelson Whittington.

15 And I would like to say that I initially, after
16 some success with lamivudine, took it upon myself to
17 contact Dr. Brown at Glaxo Wellcome to personally say thank
18 you and offer my assistance at any time. And here I am
19 today, and I appreciate their assistance in my
20 transportation to come here and speak to you today.

21 I want to thank you for the opportunity of
22 speaking about a subject that is near and dear to my heart
23 and my liver. I also speak on behalf of all who are
24 currently suffering with the disease of hepatitis and its
25 many consequences. I consider it a great honor to share

1 with you an overview of my situation and how lamivudine has
2 drastically altered my life.

3 You have been presented with a great deal of
4 documentation regarding the research, the studies and facts
5 of what I like to call a wonder drug. I am in no way a
6 physician or doctor of pharmaceutical research, nor do I
7 even understand how lamivudine works, but I am a person
8 that represents one of the statistical facts that is before
9 you.

10 I'm a musician whose world collided with the
11 medical profession in December of 1993 when I was diagnosed
12 with chronic hepatitis B. Before my diagnosis, I was a
13 person who never got sick. I very rarely even got a cold
14 or a sniffle, and was fortunate to still have all of my
15 original parts, my wisdom teeth, tonsils, appendix, et
16 cetera. Of course, at the age of 39, I was not too sure
17 about the amount of warranty left on any of them.

18 I initially went to my doctor with what I now
19 recognize as symptoms of cirrhosis, and after some testing,
20 they determined the cause, hepatitis B, with a viral count
21 in the millions. According to the doctors, I had
22 contracted the disease over a decade prior and, as my
23 health goes, never displayed any symptoms whatsoever, not
24 even jaundice. With chronic hepatitis and 80 percent of my
25 liver compromised, the future was not very promising.

1 I was told from the first that lamivudine was
2 being researched, but I had a platelet count that was far
3 below the hospital protocol minimum of 100,000 to be
4 included. The final analysis was that I had about 1 year,
5 maybe more, to enjoy life and get my affairs in order.
6 Needless to say, I was devastated.

7 After getting over the initial shock, I
8 proceeded to get a second, third, and yes, even fourth
9 opinion. They were all the same. Several months had
10 passed, and I remembered the name lamivudine from my
11 original diagnosis and made phone calls all over the world
12 trying to get the drug and at least try to do something
13 because with chronic hepatitis no liver would ever be
14 granted.

15 Obviously, I finally got FDA approval to be
16 included on the study on a compassionate basis and the drug
17 was in my hand by late October of 1995. Do the math. By
18 this date, I was already on borrowed time. I began daily
19 doses immediately, and while taking lamivudine, monitoring
20 blood tests were set for the next 6 months to follow its
21 progress. The first test in 4 weeks and then every 2 weeks
22 thereafter.

23 4 weeks later I did take my first test and the
24 results read negative. The second test was taken the next
25 day to ensure a correct response, and it as also negative.

1 I was, as were the doctors, extremely surprised and elated.

2 Thinking positively, as I do, that lamivudine
3 would be a success, I had already made tentative
4 arrangements for transplant. Just 5 days after those test
5 results, December 5th, 1995, I was on a plane to
6 Northwestern Medical Center in Chicago to start the vigil
7 for a liver.

8 Call it whatever you like, luck, good fortune,
9 or a miracle, but a matching donor organ became available
10 only a month later, and transplantation took place on
11 Tuesday, January 8th, 1996. The following Friday, just 3
12 days after my surgery, I was doing so well they discharged
13 me from the hospital. January 21st I flew home to Florida,
14 still donning my stitches. By mid-February I was driving
15 again and able to resume some sort of normal life.

16 Well, here I am today, 2 years and 9 months
17 later, speaking to you with a blood report that would make
18 most healthy people green with envy. To date my viral
19 tests continue to be negative. In fact, 4 months ago, the
20 doctors told me that my tests were actually showing signs
21 of immunity.

22 As I mentioned before, I'm a musician, a
23 singer, and conductor. Since my transplant, I have lived
24 every day with a renewed enthusiasm in my personal as well
25 as professional life. In the last couple of years I have

1 performed for approximately 100,000 people in one capacity
2 or the other, most of it while touring the State of Florida
3 singing as one of the three Florida tenors. I also do many
4 other performances on my own, making time for occasional
5 appearances for Transplant Foundation fund raising events.

6 However, there is no doubt in my mind that the
7 most meaningful performances were in June of 1996, only 5
8 months after my transplant, when I was able to sing for the
9 celebration of my parents' 50th wedding anniversary and
10 also April of 1997 when I was fortunate to sing for the
11 wedding of my youngest brother Jeff.

12 Singing for thousands of people, my family, and
13 being able to complete my life and fulfill my dreams is all
14 directly linked to medical research, a drug called
15 lamivudine, and an anonymous organ donor, and a medical
16 community dedicated to better health for America.

17 I want to conclude by thanking you again for
18 the opportunity to speak today. At this point in my life,
19 I feel I have received an unexpected medical education, and
20 especially today, and deserve some kind of diploma. Well,
21 I have my diploma and I carry it with me every day right
22 next to my heart. It's my new liver. Words could never
23 express the happiness I experience each day knowing that I
24 do have a tomorrow.

25 Today I want to share with you my hope that

1 | this drug, an opportunity for life, may continue into the
2 | future granting multitudes of afflicted people the same
3 | positive results that I have experienced. I really
4 | consider lamivudine to be a true gift of life.

5 | DR. HAMMER: Thank you very much for those
6 | comments.

7 | Alan Brownstein?

8 | MR. BROWNSTEIN: Good afternoon. I am Alan
9 | Brownstein. I'm the President and Chief Executive Officer
10 | of the American Liver Foundation.

11 | ALF is a national voluntary health agency
12 | dedicated to preventing, treating, and curing hepatitis and
13 | other liver diseases through research and education. We
14 | are made up of patients and families, as well as medical
15 | and scientific leaders organized through chapters
16 | throughout the United States. I wish to disclose that over
17 | the past 3 years ALF has received unrestricted educational
18 | grants from Glaxo Wellcome in support of our educational
19 | programs.

20 | I am joined here today by Mary Gong Sweeney of
21 | Pittsford, New York and Ralph Difonzo of Douglaston,
22 | Queens. They have come down here to share their personal
23 | stories as patients who have been afflicted with chronic
24 | hepatitis B.

25 | We are pleased that you are reviewing the new

1 drug application for lamivudine for the treatment of
2 chronic hepatitis B. We are not here today, however, to
3 speak to the safety or efficacy of lamivudine, but rather
4 to speak to the urgency concerning chronic hepatitis B and
5 the need for expeditious review for all therapeutic agents
6 considered for the treatment of chronic hepatitis B.

7 As you know, hepatitis B is a major cause of
8 chronic hepatitis, cirrhosis, and hepatocellular carcinoma.
9 There are more than 1.2 million Americans with hepatitis B
10 infection and an estimated 15 to 25 percent will die of
11 related complications. That gets translated to 6,000
12 deaths per year.

13 According to the World Health Organization, as
14 you heard from the previous speakers, this is an epidemic
15 that is ravaging other parts of the world to the extent
16 that there are more than 1 million lives taken each year.

17 As you also know, at this time alfa interferon
18 is the only FDA approved therapeutic agent known to have a
19 lasting beneficial effect in the treatment of chronic
20 hepatitis B. This treatment has been known to produce
21 long-term remission in only 25 to 40 percent of the
22 patients who have taken it. Thus, there is a dire need for
23 more treatment options for the majority of patients with
24 chronic hepatitis B who do not respond to interferon
25 therapy.

1 Without further therapy, many more will go on
2 to die, and those who are more fortunate will receive liver
3 transplants, as we've just heard.

4 We are optimistic with the development of
5 additional antiviral therapies, one of which, lamivudine,
6 you are reviewing here today. We are hopeful that
7 nucleoside analogs will help a number of patients who do
8 not respond to interferon alone. We are grateful that you
9 are giving all your attention to this in your review here
10 today. We are also optimistic about the future, about
11 other approaches, immune-directed and molecular, that are
12 in the pipeline which you'll be reviewing in the future.

13 In closing, we thank you again for your
14 attention to hepatitis B and your understanding that there
15 is a critical need for new therapeutic options.

16 I am now honored to read a brief statement from
17 Mr. Edmond Blake who was unable to join us here today, and
18 this is to the Food and Drug Administration.

19 "In 1973, I contracted hepatitis B which
20 subsequently became chronic. I was treated twice with
21 interferon. The first time succeeded in bringing down SGPT
22 and SGOT enzyme counts, but they went back up after
23 treatment termination. The second treatment had similar
24 results. In subsequent years, my condition deteriorated to
25 the point that in June 1993 the prognosis was cirrhosis,

1 cancer, or even early death.

2 "After waiting 6 months, I received a liver
3 transplant in December 1993, about the time when I may have
4 had a week or 2 to live. The liver transplant was highly
5 successful, and all the tests since have shown a normal,
6 healthy condition. However, I must receive costly
7 hepatitis B immune globulin, HBIG, infusions every 2 months
8 to prevent hepatitis B from attacking the new liver.

9 "Needless to say, if a drug is successfully
10 developed and utilized soon to remedy chronic hepatitis B,
11 thousands of lives may be saved with considerable financial
12 savings from the costly procedures I went through of over
13 \$500,000. The need is great and the time is short."

14 That's signed from Edmond Blake of New York
15 City.

16 Now I have a special honor of introducing to
17 you Mary Sweeney and Ralph Difonzo. Mary.

18 MS. SWEENEY: My name is Mary Gong Sweeney and
19 I am a chronic hepatitis B carrier. I would like to share
20 with you how I came to learn that I have hepatitis B.

21 In 1985 my brother Jim was diagnosed with liver
22 cancer. He was prompted to medical attention when he
23 experienced shortness of breath. Being an athlete and a
24 nonsmoker, he found this very disturbing. Further tests
25 revealed that he had liver cancer caused by the hepatitis B

1 virus. 2 and a half months later, he died at the age of,
2 36.

3 At this time it was recommended by the doctors
4 that the entire family be tested, and we all tested as
5 positive carriers as well. We were put on a testing
6 regimen that consisted of blood tests and ultrasound every
7 6 months, and in spite of being tested, 2 and a half years
8 later, my mother was also diagnosed with liver cancer. 2
9 and a half months later, she passed away at the age of 62.

10 At that time our testing regimen was changed to
11 the blood tests and ultrasound tests done on alternate 6
12 months so that every 3 months one test or the other was
13 done to track and slight changes.

14 My mother died feeling very guilty and
15 responsible for having infected her family, and I'll always
16 regret that I was not able to explain the situation to her
17 more thoroughly.

18 Anyway, it was at that time that as a result of
19 the blood tests, I began to show a pattern of fluctuating
20 enzyme levels. I was referred to a liver specialist who
21 recommended interferon therapy for me. It was explained up
22 front that the chances for success were very low for
23 someone like myself who has been a carrier for many years.
24 The interferon therapy failed. After 2 months it was
25 obvious that it was not having any effect, and at 3 months

1 I was taken off of the drug. At that time my hair started
2 falling out, and I lived with that for 2 years before I
3 finally gave in and had it all cut off.

4 At the failure of the interferon, I luckily had
5 another option and that was antiviral therapy with
6 lamivudine. I have been taking 150 milligrams daily for 3
7 or 4 months now, and presently I'm awaiting test results
8 from some blood work. Depending on those results, I may be
9 taken off of lamivudine.

10 I'm eager to have other options available to
11 me. If the lamivudine doesn't work, I need to have other
12 options. Without other options, I feel like I'll be up
13 against a brick wall, and without other options, I'll be
14 looking at my carrier status of the virus as a time bomb
15 waiting to go off. So, I hope to not have to deal with
16 that.

17 Thank you for your time.

18 MR. DIFONZO: Good afternoon. My name is Ralph
19 Difonzo. I'm 63 years old.

20 In 1994, the early part of January, I was
21 diagnosed to have hepatitis B, cancer, and cirrhosis.
22 After long procedures, I was able to get on a waiting list
23 of liver transplant. December 29th, 1994, I was blessed.
24 I received a transplant. 6 months after that, I was able
25 to have a normal life. It was really great. It was

1 | wonderful.

2 | I was receiving an infusion of HBIg every 2
3 | months, and it was okay for about 6 months. At the end of
4 | the year, exactly December the 29th, we had a rejection.
5 | We took care of that and we went on for another 6 months.

6 | And at the end of July 29th, 1996, I received
7 | an HBIg infusion. We used to get one every 6 weeks. The
8 | next one would be September the 15th. However, there was
9 | none available. I was left without a medicine for about 3
10 | weeks, which at this point my liver became infected. So,
11 | we had to go through the whole procedure again. I was
12 | fortunate enough to recuperate, recover from it.

13 | In 1997, in March, my doctor put me on one
14 | monthly infusion, every 30 days infusion, of HBIg and also
15 | 450 milligrams of Epivir. I had 18 months. It was just
16 | wonderful. I'm having a normal life, and I'm the happiest
17 | man on the face of the earth.

18 | Please approve this medication.

19 | My concern is 4 years ago I used to take the
20 | infusion every 2 months. 2 years later I was taking it
21 | about every 6 weeks. Now we're down to a monthly infusion.
22 | What's going to happen 2 years down the road? So, we would
23 | like, if it's possible, some other options, if that's
24 | possible.

25 | Thank you very much. Have a good afternoon.

1 DR. HAMMER: Thank you very much, and on behalf
2 of the committee, I'd like to thank all of the speakers at
3 the open public hearing for their eloquence and impassioned
4 statements.

5 Before we close the open public session, no one
6 else has signed up, but if someone does want to speak, this
7 is the opportunity to come forward.

8 (No response.)

9 DR. HAMMER: If not, the morning session is
10 closed. We'll reconvene at 1:30. Thank you.

11 (Whereupon, at 12:33 p.m., the committee was
12 recessed, to reconvene at 1:30 p.m., this same day.)
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AFTERNOON SESSION

(1:35 p.m.)

DR. HAMMER: Can I ask the committee members to please convene at the table so we can start?

Thank you. I'd like to convene the afternoon session for our discussion for the indication for the treatment of chronic hepatitis B.

We have some time, a few minutes, for the committee members to direct questions to the FDA presenters, in case there are any. I'm not going to specifically go around the table, as I did this morning, but will allow people to ask sporadically as the need arises. So, does anyone have questions specifically for the FDA presentation? Henry?

DR. MASUR: Dr. Styrt, actually I was very intrigued by a number of aspects of your analysis. But in terms of the response of the Oriental cohort as opposed to others in terms of surrogate marker, were there any predictors from baseline variables that would have suggested why that cohort had a better DNA response than the other cohorts?

DR. STYRT: Well, there certainly are a number of things that are different about the group that was enrolled in that study as a group. For example, they were not required to have as much evidence of liver inflammation

1 by biopsy or by ALT to be enrolled in the trial, and a
2 small proportion of them had previous experience with
3 interferon, although most of the were treatment-naive. And
4 clearly there were differences in the mode of acquisition
5 of disease and presumably could also be differences in
6 genetics either of the host or of the virus. But in terms
7 of other specific predictors -- the applicant may also want
8 to comment on this -- we didn't have other specific
9 baseline variables that seemed to predict the differences
10 in response.

11 DR. HAMMER: Does the sponsor want to add
12 anything to that?

13 DR. BROWN: I think the term "difference in DNA
14 response" was used. We didn't fundamentally see that. It
15 may have been because we looked at the data a little
16 differently, but we did do some regression modeling of
17 things like seroconversion, for example.

18 DR. MASUR: I'm sorry. You didn't see a
19 difference in durability of response?

20 DR. BROWN: Correct. The FDA did look at the
21 data a little differently than we did. We had analysis
22 called sustained HBV DNA response, and I don't know if
23 that's worth putting up, but in a nutshell, there was a
24 marked difference between drug and placebo in both the
25 Asian multi-center trial and the U.S. multi-center trial

1 and the other placebo-controlled study in what we analyzed
2 as sustained DNA response. That was specifically patients
3 with detectable DNA at baseline achieving a negative value
4 and then maintaining negativity to the end of week 52. DNA
5 response -- did we keep it as 2 or 1? Sustained was at
6 least 2 and then to the end of treatment.

7 There were some differences across studies, but
8 when we did some regression modeling of baseline factors
9 for things like e loss and e conversion, ethnic origin did
10 not come up as predictive in those kinds of analyses of
11 predictors of sustained response. That's really the point
12 I wanted to make.

13 DR. HAMMER: Please.

14 DR. HAMILTON: So, these are the tough
15 questions coming up now.

16 Not being a hepatologist, I don't actually see
17 that many patients with chronic hepatitis B and would defer
18 to the comments I think of my associate on the panel, who I
19 know is a clinician with chronic hepatitis B, and maybe
20 others to further characterize for me and maybe for others
21 what these people's clinical conditions are. I know we
22 heard this morning, as Scott said, some impassioned and
23 important testimonies as to the impact of hepatitis B on
24 their lives. But it's my sense that hepatitis B that's
25 chronic in the majority of individuals is not quite that

1 | dramatic. I guess to that end, A, I'd like to hear some
2 | commentary about what a typical population of patients
3 | might be like or in fact specifically if the sponsor can
4 | give me some sense of what their clinical condition was,
5 | and how that clinical condition in some objective manner
6 | was modified by this year or so worth of therapy.

7 | There has been an accounting of what the
8 | adverse side effects were and so on, but I guess I'm
9 | looking for something a little more global, a little more
10 | realistic that I think of when I'm talking to a patient in
11 | the clinic. You know, how are you feeling, and X, Y, and
12 | Z? I don't think of them in terms of placebo or active
13 | control study modes but as people.

14 | So, I guess the question seems a little vague
15 | probably, but does the sponsor have some clinical data that
16 | would be of use to me in thinking in terms of how useful
17 | this drug is going to be in real terms to the patient?
18 | Because the patient, of course, doesn't give a rip if his
19 | ALT is twice normal or if his viral load is 3 logs down or
20 | anything like that. He wants to feel better. So, were
21 | there quality of life measures, for example, that would be
22 | useful in assessing this?

23 | And there are some other kind of derivative
24 | questions, but maybe I'd start off with that one. Maybe
25 | before they respond, Blaine, maybe you could help me

1 understand what these patients are like.

2 DR. HOLLINGER: Well, I could, John, but there
3 are a couple of people the sponsor has here who have been
4 involved in some of these studies such as Terry Wright and
5 Bob Perrillo and Jules Dienstag who actually have admitted
6 these patients into these studies. Because I agree with
7 you. I think it would be nice to know what they are.

8 The bottom line is like hepatitis C, many of
9 them have no symptoms initially -- and that's one of the
10 problems with these diseases -- until they develop really
11 serious end-stage liver disease. But maybe they want to
12 answer that question because they had to make a choice for
13 that.

14 While they're doing that, they might also
15 comment along this same line, if you could, about these
16 missing values, like the biopsies. Why were these biopsies
17 not done? Was it because they had bad disease like
18 cirrhosis? They chose not to biopsy them, which could then
19 bias the study? Or were there other reasons that this data
20 was missing either for biopsies or for blood samples at the
21 week 52?

22 DR. DIENSTAG: The biopsies were missing
23 because second biopsies in clinical trials of this sort by
24 definition are for research purposes, and many patients
25 decline to have the second biopsy done. In some cases,

1 | whether a patient is willing to have a second biopsy is
2 | determined largely by their experience with the first
3 | biopsy.

4 | As far as the impact on patients, I think most
5 | patients with chronic hepatitis B, at least the ones we see
6 | in our studies of patients who have compensated disease,
7 | are pretty healthy. Some of them have chronic fatigue that
8 | limits their ability to function, but the important thing
9 | about hepatitis B is that in the presence of ongoing virus
10 | replication, the disease tends to be an ongoing one
11 | associated with liver injury. There are long-term follow-
12 | up studies in such patients, and in some studies the 5-year
13 | survival can be as little as 50 percent in patients with
14 | severe chronic hepatitis B. In those studies, the patients
15 | who are the ones with the most severe disease are the ones
16 | who have the highest level of virus replication. This is
17 | somewhat analogous to hepatitis C which is a progressive
18 | disease, but here, where replication occurs, there is
19 | ongoing liver injury and there's a very nice correlation.

20 | It's very difficult to show an improvement in
21 | quality of life during the course of a trial of this sort.
22 | Now, if you take interferon, on the other hand, patients
23 | who come into clinical trials who feel reasonably well,
24 | feel pretty bad during therapy. And there it's even more
25 | difficult to show quality of life improvements because they

1 | feel much worse on therapy than off. Here we're not
2 | dealing with that. Patients don't even know they're taking
3 | the drug.

4 | I don't know if that satisfies your inquiry,
5 | but it is a progressive disease and it may not be
6 | progressive in a month or 2, but over the course of several
7 | years it can be a very devastating disease.

8 | DR. HAMMER: Jules, please state your full name
9 | and affiliation for the transcript please.

10 | DR. DIENSTAG: I'm Jules Dienstag. I'm a
11 | hepatologist at Massachusetts General Hospital, a clinical
12 | investigator for these trials. I guess in a sense I'm here
13 | as a consultant today.

14 | DR. WRIGHT: I'm Teresa Wright. I'm also a
15 | hepatologist. I've also run trials with Glaxo Wellcome.
16 | I'm Chief of GI at the VA in San Francisco and Associate
17 | Professor of Medicine at UCSF.

18 | Dr. Hamilton, it's actually rare as a
19 | clinician, as a physician, as opposed to a surgeon, to see
20 | an intervention that makes a difference. We have gone over
21 | the last 6 years from not being able to transplant patients
22 | with hepatitis B infection to the point now where they are
23 | superb candidates for liver transplantation. The only
24 | reason that we've been able to do that is the availability
25 | of nucleoside analogs. The only one we have experience

1 with so far is lamivudine and also with the use of high
2 dose hepatitis B immune globulin. So, it has been an
3 enormously gratifying experience over the last 6 years
4 where we have been able to take people who have no option
5 therapeutically to give them an extremely good outcome.
6 So, that is the transplant patient.

7 In the chronic hepatitis B patient, I think
8 Scott Lincoln's testimony this morning about the
9 improvement of his PAN is actually quite unusual. That's
10 not a group of patients that we have studied. I think most
11 patients with chronic hepatitis B have a good quality of
12 life. Many are asymptomatic, but we know that this virus
13 in man is associated with death in about 50 percent of the
14 time.

15 So, I think there is no doubt about the ravages
16 this virus causes, and I just hope that this is just one of
17 many therapies which are going to allow us to stabilize
18 disease, reverse disease, and hopefully prevent the need
19 for liver transplantation. So, I think there are many
20 reasons that we as hepatologists are very encouraged by
21 being involved in these trials. Thank you.

22 DR. PERRILLO: I'm Bob Perrillo and I'm head of
23 the GI and Hepatology Section at the Ochsner Clinic.

24 I've dedicated the last 18 or 19 years to
25 antiviral therapy of hepatitis B, and I've seen many of the

1 | things that the other two physicians have just alluded to.

2 | I'd like to point out that with the
3 | decompensated patient population, not only are they more
4 | likely to be symptomatic, but they have less viable
5 | options. They don't have a lot of time. We don't have to
6 | calculate it in 5-year survivals. It could be shorter than
7 | that.

8 | Interferon is something I've had first-hand
9 | experience within these patients. A few years ago, we
10 | published that on a multi-center trial looking at
11 | decompensated hepatitis B. It's a very, frankly, dangerous
12 | therapy in many of these patients. It leads to immunologic
13 | activation, flaring of their ALT, and it's a real trial by
14 | fire. So, we have had another option provided to us in
15 | lamivudine. So, even going beyond quality of life indices,
16 | we now have a safer approach to managing these patients.

17 | I think the other thing I'd like to draw
18 | comment to is that we not lose sight of the fact that in a
19 | perfect world, yes, we would have everyone appropriately
20 | vaccinated, but that simply doesn't exist. These people
21 | are infectivity reservoirs for the community and that leads
22 | to actually many of the young, predominantly male patients
23 | I see being morally devastating by the fact that they know
24 | that they're infectious for intimate contacts. So, we now
25 | have an option, a safer option than interferon for the

1 | decompensated patients and an equally effective option in
2 | the non-decompensated population to limit this infectivity
3 | situation.

4 | Thank you.

5 | DR. HAMMER: Thank you.

6 | Ms. Melpolder, did you have a question?

7 | MS. MELPOLDER: I had an observation about the
8 | Asian population, in addition to the sustained HBV DNA data
9 | that FDA presented. It seemed that they had about half the
10 | incidence of mutation that the other studies showed. I
11 | just wondered if there was some genetic predisposition that
12 | prevented the mutation of the virus in the Asian
13 | population.

14 | DR. HAMMER: Does anyone want to tackle that
15 | challenging question?

16 | DR. BROWN: I think the correct term is
17 | exploratory analyses. We've done a number of exploratory
18 | analyses of these kind of data, and when we did some
19 | regression modeling, using kind of a standard set of
20 | potential baseline covariates, we did in fact find in a
21 | sense -- these have to be considered kind of post hoc or
22 | retrospective observations, if you will, that would
23 | certainly need prospective confirmation. It didi appear
24 | that the Asian versus caucasian did signal a lower
25 | incidence of YMDD variants if you will in Asians versus

1 caucasians.

2 When we removed that as the first observation,
3 the first level in the multivariate, then we did see
4 potential impact of others, but these are oftentimes not
5 reaching statistical significance and need to be considered
6 exploratory. That's a fancy way I think of saying we don't
7 know why, but we do seem to see a little bit lower
8 incidence of the YMDD variants in the Asian population even
9 after adjustment for some of the covariates such as all the
10 standard kind of diseases associated covariates.

11 DR. HAMMER: If I could ask a corollary
12 question. How sensitive is the assay to picking up
13 mixtures of mutants? Your PCR assay of looking for the
14 YMDD mutation, what proportion of mixtures can you pick up?
15 20 percent, 50 percent?

16 DR. BROWN: The overall threshold level of
17 detection in Dr. Condreay's assay was approximately 1,000
18 genomes per ml. Then as I mentioned, the typing is
19 actually done by an RFLP based assessment. So, mixed virus
20 -- basically when the mutant is present at a 5 percent or
21 greater level within the total population, it is
22 detectable. And what we called mixed was anywhere between
23 5 and 95 percent because you can see, in a sense, both
24 bands in the gel I guess is the colloquial way to say it,
25 whereas at less than 5 percent mixed, of course then the

1 mutant becomes the fully mutant.

2 DR. HAMMER: Have experiments been done for
3 individual clones to try to be more sensitive as to whether
4 you've got mixtures or --

5 DR. BROWN: No. I think we can say we haven't
6 done multiplex cloning and that sort of thing.

7 DR. STANLEY: Dr. Hammer, as I understood Dr.
8 Styrt's data, though, when they analyzed it after the week
9 104 follow-up, there was about 42 percent resistance in the
10 Asian population. So, it would appear to maybe just be a
11 delay as opposed to an actual decreased level.

12 DR. BROWN: That's certainly possible.

13 DR. EL-SADR: I'm wondering. I'm going back on
14 the dose again. Is it possible that somehow the Asian
15 patients are smaller in size or something about the dose
16 and you're able to sustain a higher level? The whole thing
17 is sort of level of drug, suppression of virus, prevention
18 of resistant mutants.

19 DR. BROWN: That's an excellent thought. We
20 did put body size parameters into the multi-step regression
21 modeling and the weight and height and body mass index were
22 factored into it. But the Asian versus caucasian
23 assessment came up independent of body mass index.

24 DR. EL-SADR: How about pharmacokinetics? Do
25 you have some pharmacokinetic data in that population?

1 DR. BROWN: We do in fact. The PK data might
2 Dr. Bye want to speak to that, but it looks remarkably
3 similar to PK in westerners.

4 DR. BYE: Dr. Bye, Glaxo Wellcome.

5 We did a population kinetic analysis and there
6 was no difference between the caucasian and Oriental
7 subjects, and we also did a high powered bioequivalence
8 type study, again there was no difference comparing against
9 caucasians and Orientals. So, I don't think it's a PK
10 issue.

11 DR. HAMMER: Dr. Sjogren.

12 DR. SJOGREN: I'm sitting here and wanting to
13 rise to the challenge that Dr. Hamilton set up thinking as
14 a hepatologist more than a researcher. I work at Walter
15 Reed just a few blocks down the road, and I've been there
16 since 1981. So, I've seen clinic patients with hepatitis B
17 way before any kind of therapy was available, where we
18 could only follow them or study the natural history and see
19 them, indeed, get in trouble very often.

20 Then as interferon came along, where we've all
21 worked with it and we are satisfied when a third of the
22 patients respond, but then obviously the other two-thirds
23 are out there with their hepatitis B that cannot be
24 controlled.

25 In my population, a lot of the people that I

1 see are young, just by virtue that they're in the Army, and
2 when you get all the older, the Army doesn't want you
3 anymore. You got to go. So, I see a lot of these patients
4 with active hepatitis B that don't respond to interferon.

5 I've never worked with Glaxo. This is not a
6 complaint.

7 (Laughter.)

8 DR. SJOGREN: It's just stating the fact.
9 Indeed, I was not able to secure a compassionate use
10 protocol with them. So, I'm pretty objective I think.
11 They don't owe me nothing. I don't owe them anything.

12 But my hospital has Epivir because we treat HIV
13 patients, and so I reach out to lamivudine as a
14 hepatologist and with great concern, but at the same time
15 evaluating the last 2 years that it has been available to
16 us and noticing that my patients did get better. The ALT
17 got better. The DNA disappeared in a great proportion of
18 them. I haven't biopsied all of them as the studies have
19 shown, but listening to the presentations and reading their
20 material, I observed that the liver histology has improved.
21 So, all I know, I come away thinking this is a good drug.
22 This is a good alternative.

23 I still have a lot of questions that need to be
24 answered. I think the treatment with interferon is one of
25 them. The long-term therapy is another one, and some

1 others that probably we'll discuss later this afternoon.

2 But I know in my young patients and in my older
3 patients that the drug is providing a hopeful therapy in
4 terms of reducing the DNA and, as I understand now,
5 improving the histology. I'm disappointed that the
6 serology is not any better, but at the same time I am
7 understanding that the serology may not be all what we have
8 thought it would be. They may not be the clinical
9 parameters to follow, that we still have a lot to learn.

10 But like I said before, in rising to the
11 challenge of thinking as a clinical doctor, I think
12 lamivudine offers a definitive hope to some patients where
13 there was nothing to be done for them in the past.

14 DR. HAMMER: Thank you.

15 Blaine?

16 DR. HOLLINGER: Scott, I've got some comments
17 and some observations. This is of questions, if I could
18 please.

19 The comment, first of all, I think is what Dr.
20 Perrillo said, is we should never lose sight of the fact
21 that, distinct from HIV, HBV does have a vaccination, and
22 we should never lose sight of the fact that the control of
23 this throughout the world is going to be elimination of
24 hepatitis B. Then we don't have to worry about whether
25 these drugs work or not and how well they work. So, we

1 | should always push for that.

2 | Now, having said that, on some of the FDA's
3 | work that was presented, the impression that I got in
4 | looking at the data was that the sponsors probably have not
5 | reached the optimal endpoint at week 52. Most of the data
6 | was still climbing at the end of week 52. Yet, at the same
7 | time, there seemed to be an increased development of
8 | resistance going on, and at some point these are probably
9 | going to cross. Therefore, you may have less effectiveness
10 | going on because there's more resistance being developed.

11 | I guess the question would be -- again, it has
12 | been asked -- is whether longer treatment or higher dose
13 | are better in this case. I think you presented some data
14 | from 3018 that maybe did not show this, suggested it did
15 | not seem to be much better at 2 years. But this is a very
16 | important issue because if resistance does develop and if
17 | you can suppress viral replication early, very early, with
18 | higher doses, then you might suppress the development of
19 | resistance.

20 | Now, I know there are some papers. For
21 | example, I think there is a paper being presented at the
22 | AASLD coming up which suggests that that may not be the
23 | case, that actually the half-life may be fairly similar in
24 | patients who got higher doses of lamivudine than those that
25 | got lower doses of lamivudine.

1 But, first of all, could you respond perhaps,
2 or even the sponsor might respond first of all, about the
3 dosage, the duration, and something of that order?

4 DR. BROWN: I mentioned on a slide -- I think
5 it was called principal dose findings -- that in fact using
6 either the conventional hybridization assay or PCR, we
7 don't see any really appreciable difference in antiviral
8 effect at doses in adults above 100 milligrams per day.
9 The PCR data we have in adults extends essentially out to 6
10 months. In that particular European 6-month study, the
11 doses that were compared were 25, 100, and 300. We have
12 that data on a slide, but the bottom line is even when you
13 use PCR levels, we don't see a difference in clearance of
14 virus, if you will, at doses above 100.

15 I also mentioned that we don't see a difference
16 in incidence of YMDD variants either in the progression
17 modeling by dose, I should say, or drug concentration for
18 that matter. We don't see a difference in YMDD variants in
19 the regression modeling where dose was factored into it,
20 nor did we see a difference in the Asian multi-center trial
21 between the 25 and 100 milligram cohort. At 1 year in the
22 25 milligram, it was 14 percent incidence, and 16 percent
23 in the 100, but that was very similar not statistically
24 distinguishable.

25 But certainly I think we certainly agree, and a

1 major issue I think obviously for discussion is treatment
2 duration. Here's the result of discontinuing lamivudine
3 arbitrarily at 1 year for the purposes of studying the drug
4 in patients with chronic hepatitis B. What we've displayed
5 here are the post week 52 data across the three studies in
6 which there as a lamivudine 100 milligram patient cohort,
7 and placebo is illustrated in yellow.

8 First thing important to point out is -- I
9 think it was emphasized perhaps in the FDA's presentation
10 -- there is a decline in HBV DNA levels in placebo
11 patients. And during the first year we showed that on our
12 core presentation as well. That has actually been observed
13 in the 3-month adefovir study recently reported as well.
14 We think there may be regression of the mean operating in
15 this disease that has a somewhat cyclic nature, but that's
16 a speculation.

17 In any case, here's the placebo HBV DNA in the
18 post-week 52 period, so to speak, looking about level.
19 Here's what happens in the cohort. I mentioned we had an
20 exploratory cohort in the interferon nonresponder study
21 where patients stayed on drug, and this is their median HBV
22 DNA level on that treatment arm where they stayed on out to
23 the end of study at week 68. Here's the rest of the
24 patients from the European/Canadian study, as well as the
25 U.S. study, and half of the patients on this study who went

1 on to either placebo or just discontinued from treatment at
2 week 52, again showing, as we observed in phase II, that
3 the disease does come back in this case over a 4-month
4 post-treatment period. So, the continuously treated
5 lamivudine group in this kind of analysis did better with
6 regard to viral load.

7 We have an ALT curve that basically shows the
8 same kind of phenomenon with the ALTs tending to come back
9 up towards placebo ALTs when you arbitrarily discontinue at
10 1 year.

11 DR. HOLLINGER: Yes, I see that, but again I
12 think what Dr. Styrt presented was data with the
13 seroconversion and that looked like that continued to
14 improve as time goes on. I think the bottom line is you
15 really don't have data which compares 100 with 300 for a
16 year to look at whether there is a reduction in the
17 variants or the response rate. Is that correct?

18 DR. BROWN: It's correct that we do not have
19 300 milligram dosing data for a year because of the
20 considerations I mentioned. 100 milligrams was chosen as
21 the phase III dose. I'll stop there.

22 So, with regard to effects of longer therapy on
23 e conversion, we mentioned that we felt we were seeing some
24 additional effects. In the 3011 study, we and the FDA
25 mentioned that we didn't feel we had achieved statistical

1 significance for seroconversion in interferon
2 nonresponders, whereas in treatment-naive patients in the
3 Asian and U.S. study, it did appear as statistically
4 significant. This is the 3011 study, and the
5 seroconversion rate at week 68 in this study for the
6 continuously treated patients was 24 percent compared to
7 the 18 percent which we showed for week 52. So, that's
8 another little bit of evidence where we think there may be
9 some cumulative seroconverting effect. Actually in that
10 study placebo stayed about the same. So, the difference
11 between drug and placebo did get greater at week 68 in that
12 study.

13 But I mentioned the paradox on that study was
14 that that interferon nonresponder study actually had the
15 highest e antigen loss rate at 1 year. So, the question is
16 in this patient population, do they have a somewhat delayed
17 development of antibody to e which affects the analyses of
18 full conversion?

19 DR. HOLLINGER: While you're still there, have
20 you had a chance to look at anything regarding the
21 development of HCC in any patients?

22 DR. BROWN: No. We certainly have not been
23 able to observe any kind of differences, and we saw no HCC
24 in the core studies. It's an issue that I think we're
25 certainly interested in looking at for some of the long-

1 term clinical outcome studies that we're anticipating.

2 DR. HOLLINGER: The other thing, I think an
3 observation on the data that the FDA presented. It has to
4 do with the seroconversion status versus histology. In a
5 couple of slides, I think it was noted that even though
6 some patients did not meet seroconversion criteria, many
7 still showed histological improvement. And I wondered
8 whether there might be a threshold for histological
9 improvement that doesn't involve the absence of HBV DNA.
10 Actually that would indicate potentially that you could
11 have some HBV DNA replication going on and still generate a
12 good histological improvement both in fibrosis, as well as
13 the necroinflammatory response.

14 DR. BROWN: We do have a slide that actually
15 the basic impact of which is similar to what Dr. Soon
16 showed. Dr. Soon, if I interpreted the presentation
17 correctly, showed that there's a pretty tight association
18 between the seroconversion and histologic response, if you
19 were using that kind of response definition. But he also
20 showed that in patients who didn't have e conversion or
21 serologic response, if you will, he showed histologic
22 response in 21 of 37, which boils out to 56 percent, and
23 that's very similar to our analysis as well.

24 We looked at the composite phase III data for
25 patients who were still positive for e antigen at week 52

1 different because we don't know enough about the viral
2 pathogenesis, given the limitation on the assays. A
3 confirmed e antigen seroconversion does have some clear
4 relationship to durability, and that's probably the only
5 data we have.

6 Development of viral resistance at the moment
7 is worrisome, but the data show that those patients at
8 least in the limited follow-up still are doing better.
9 They're intermediate between placebo and the wild-type.
10 So, I think one wouldn't stop if one were getting a YMDD
11 mutant. One would just worry about it.

12 And as far as reappearance of viral DNA during
13 therapy, again I think it depends on the threshold of your
14 assay and assays that are looking at thresholds of 10 to
15 the 5 and 10 to the 6th are again, to quote a refrain from
16 another disease, the tip of the iceberg, and getting below
17 detectability is going to, I think, have a much greater
18 lower limit target of 100 copies when we're there.

19 Also, as far as stopping for the development of
20 resistance or reappearance of viral DNA, that's really an
21 issue of the options one has as well as the assays, and
22 when one has limited options in this disease, one is
23 probably not going to stop.

24 The optimal duration of treatment for patients
25 I think is not clear. That only will come through follow-

1 up studies.

2 The implications of resistance I think are
3 ominous. We need to know more about it, really what the
4 preexistence of viral mutants is. It doesn't seem to be
5 high, but we need to know more about the sensitivity of
6 these assays that are looking for resistance both in the
7 blood and in the tissue. It clearly is going to limit the
8 drug over time and is another reason once again to move
9 quickly into combination treatments.

10 I think that the approval of this drug is going
11 to change things because placebo controls are not going to
12 be, at least to me, permitted in this population. So, one
13 thing we have to think about is if we have new active
14 control arms, are those active control arms going to be
15 monotherapy arms for a long time or should we be, in fact,
16 thinking about novel ways to do active control arms that
17 quickly move into combination status.

18 Dr. El-Sadr raised the issue of the
19 reintroduction of treatment and whether resistance will
20 really emerge, and I would echo that. It's nice that the
21 viruses that come back after treatment stops in the setting
22 of resistance are wild-type, but we have no reassurance and
23 probably it's quite likely in this setting that resistance
24 will quickly reemerge.

25 The point about relationship of virologic and

1 serologic markers as a proxy for histologic changes. I
2 like the term "proxy" because it particularly avoided the
3 issue of surrogate markers which has taken this committee
4 around in circles in the past, but that's essentially what
5 this is about. Again, we have to improve our assays and
6 have our correlations with histologic outcome, but without
7 long-term follow-up for the longer-term outcomes, we won't
8 really know. But obviously it makes sense that if you get
9 improved ALT, drive the virus to undetectable levels by
10 hopefully newer and more sensitive assays, and get
11 seroconversions, that's all very logical and I think we
12 have enough data to make the prediction that that's going
13 to be good for patients in the long term.

14 As far as the HIV issue, I agree that it should
15 be mandated. You really can't mandate it, but one thing it
16 should be is standard of care and it also should be
17 included in the label. I'm sure it will be, but caution
18 should be exercised before Epivir for hepatitis B at 100
19 milligrams per day is prescribed, that HIV status be
20 determined.

21 One thing we should recognize, as far as this
22 goes, is patients at risk for acquisition of hep B are also
23 at risk for acquisition of HIV, as has been stated. That's
24 an increasing issue for patients not just in accident
25 situations but in other situations of sexual or other

1 exposures where people are now thinking about prophylaxing.
2 We've been prophylaxing with hep B with other things. We
3 now are prophylaxing HIV in emergency rooms and elsewhere,
4 and 3TC is a major component of that. So, it's an
5 interesting ponderable here to think about what the role of
6 this agent is in prophylaxis of hep B and when it's used
7 also to try to prophylax HIV.

8 So, I hope that helps. I think basically there
9 has been a strong consensus among the group here that we
10 need longer-term outcome, other studies, but that this is a
11 significant and important step, an incremental step, but a
12 major incremental step in the treatment of an important
13 disease and that we have learned a lot from other diseases,
14 and we need to apply that to hepatitis B and antiviral
15 therapy.

16 Is there anything else that we need to address?

17 DR. JOLSON: No. I think we really appreciate
18 all the advice that we've heard today. I think it will be
19 possible to envision phase IV commitments that will echo
20 the issues that were brought up here in terms of where
21 additional information is necessary.

22 I think the major issue for us that remains --
23 and obviously there's not available data -- is the issue of
24 treatment duration and how that's going to be approached in
25 the labeling. This is really a major departure for us from

1 the interferon model where interferon is recommended for
2 use for a certain duration of time and after which a
3 patient is observed and either has a response or doesn't.
4 And the labeling can deal with that.

5 This is going to be somewhat more difficult and
6 is really going to require I think some negotiations
7 between us and the sponsor in terms of what is the optimal
8 recommendation that can be made in the label given the lack
9 of information about the optimal treatment duration.

10 One of the problems that I foresee in
11 recommending that patients be treated until seroconversion
12 is, at least based on available data, seroconversion occurs
13 at a fairly low rate, and it may keep patients on therapy
14 who are no longer deriving benefit. Exactly how we will
15 deal with that in the label to prevent just continued year
16 after year of drug exposure in patients who are unlikely to
17 seroconvert based on response to drug, I kind of see that
18 as a challenge.

19 DR. HAMMER: I think the seroconversion is
20 perhaps one issue where we have data to suggest that the
21 response is durable, but it shouldn't be the only
22 criterion. I think this is going to have to be a flexible
23 issue in relation to other markers of response, and one
24 could list a number of markers of response. Again, as
25 assays improve, this will be helpful, but ALT,

1 seroconversion, hep B DNA. One could probably make a
2 recommendation that return to baseline in all of those
3 elements is probably evidence of lack of response or loss
4 of response, and one could stop there, but I don't think
5 personally that any single test is going to be able to be
6 used to be sure that you want to stop except perhaps the
7 seroconversion for which there is some data. But I think
8 that's likely going to be supplanted by a combination of
9 markers, including a more sensitive hep B DNA assay.

10 DR. JOLSON: So, just to make certain that I
11 understand what you're saying, then you think it would be
12 reasonable to recommend other criteria for when lack of
13 response should be considered.

14 DR. HAMMER: I think at least for the current
15 label or the imminent label, stating what the data suggest
16 as far as e antigen seroconversion is probably where to
17 start, but to say that there are other considerations as
18 far as viral markers in the absence of liver biopsy, which
19 are not going to be done routinely in the clinical setting,
20 that consideration should also be given to these other
21 markers as far as measures of response, although the data
22 do not currently exist to be certain about the long-term
23 relationship. I think there will have to be some
24 flexibility in that because, in fact, that will foster I
25 think clinical care that's more in keeping with what the

1 data suggest.

2 That's just my opinion. Others can comment.

3 DR. JOLSON: Any other parting remarks about
4 recommendations for stopping therapy?

5 DR. HAMMER: Given the expertise, particularly
6 of our guests and consultants, it just reflects that we
7 need more studies and the lack of the current database.

8 DR. JOLSON: Could I just ask one other
9 question about for future studies for this agent or other
10 agents? The way studies had been designed, and remembering
11 that these studies were designed several years ago with
12 more the interferon model in mind, with a specified
13 treatment duration, after which, at least in one or two
14 studies, treatment was discontinued and patients were
15 observed, in light of this information, do you have
16 recommendations for trial design for other agents in this
17 class?

18 DR. HAMMER: I'll start because I'll reveal a
19 prejudice. I think although it was an advance, we've been
20 hamstrung by the interferon experience and those initial
21 trials because then it became the control arm, and it
22 doesn't make sense to have this very delimited period
23 comparing 16 to 24 weeks versus 52 weeks of another agent.
24 And I would suggest that we need longer and equal treatment
25 arms as far as duration goes in future studies and that we

1 | should try to move away from the classic interferon course
2 | as the standard of care. I think the ultimate approval of
3 | Epivir will change that and for the better. I think we
4 | need longer treatments. Interferon can be moved into that
5 | in new ways perhaps, but I also think the toxicities of
6 | interferon, as we get new agents in the next 2, 3, and 4
7 | years, may move that to a second-line agent.

8 | DR. SO: I think Heidi has a tough job. Do we
9 | have enough information to say that after 3 months of
10 | treatment, if DNA does not come down at all, those patients
11 | should be taken off of treatment? I mean, it's sort of a
12 | treatment guideline as to who are responders, who are
13 | nonresponders.

14 | DR. HAMMER: I think we tried to get that
15 | question. There are some data that could be looked at as
16 | far as early changes in markers and predictors of response,
17 | and I think those data need to be culled out of the current
18 | database. One would think that if one has no early
19 | response in any marker, including hep B DNA, I would think
20 | logically it's time to think about something else if you've
21 | got it.

22 | DR. SO: Just one comment because I see a lot
23 | of patients who come to me already taking all sorts of
24 | things like shark's cartilage and all these other
25 | treatments for hepatitis B, and some of them would like to

1 stop the drug and then switch to a different agent. I hope
2 the sponsor will really clearly label or really emphasize
3 that stopping treatment unsupervised could lead to a flare-
4 up in their hepatitis because I think a lot of the Asian
5 population like to switch drugs and they might end up with
6 a big problem. Thanks.

7 DR. HAMMER: Dr. Yogev?

8 DR. YOGEV: I don't know. If you allow me. I
9 was a little bit impressed maybe more than you that the
10 interferon really didn't work, and I would encourage to go
11 into know synergy studies which we show at least in vitro
12 the two nucleosides and so forth.

13 DR. HAMMER: That's what I think I was saying
14 that interferon is going to fall by the wayside.

15 DR. YOGEV: I would encourage not to use that
16 at the start and really to go to 52 monotherapy which is
17 dual therapy just because we have the monotherapy.

18 DR. HAMMER: Well, I think it's going to be
19 combinations of interferon and Epivir, Epivir and other
20 nucleosides, Epivir and nucleotides, even three-drug
21 therapies for severe disease. I think we'll see novel ways
22 to look at these, but interferon isn't going to leave the
23 combination therapy yet. It needs to be studied in other
24 ways that disprove that it's not any better than single
25 agent therapy.

1 DR. YOGEV: And the other point is I thought
2 maybe it would be good at least to draw the attention of
3 the physician that if the HBV DNA is going up, that
4 efficacy has a tendency to be less than if they're staying
5 down. It's a point to start reassessing therapy. If we
6 won't put it in the insert, nobody would think about it.
7 They would just continue doing it because we have nothing
8 else to do. That's what we did with AZT, as you very well
9 know.

10 DR. HAMMER: That's where the new options will
11 help.

12 Blaine.

13 DR. HOLLINGER: Yes. As distinct from, say,
14 hepatitis C, in which we know there are more resistant
15 genotypes available, it doesn't seem to be that way for the
16 HBV DNA. I think we saw data today which said that the
17 YMDD is not seen in the placebo group by and large.
18 Therefore, almost all these patients respond to therapy.
19 At least their HBV DNA goes down very rapidly, within 4 to
20 8 weeks, in most patients. Now, whether there is a small
21 subgroup in there which we could look at very carefully to
22 see whether or not we could determine who will have a
23 sustained response I think is open for question. We need
24 to do that. But whether we'll find something like the 3-
25 month cut-off level like we have for interferon and HCV is

1 another issue.

2 My take-home message is that these patients
3 need to be treated probably for at least a year, and that's
4 sort of the take-home message I would have, unless they
5 seroconvert from e antigen to anti-HBe in which case, if I
6 saw that over one or two times, at least a couple of times,
7 I might feel comfortable in discontinuing therapy in that
8 individual based on the durability of the response that I
9 have seen in the data presented.

10 What I don't know is just what you've said, is
11 what do I do after a year? Because it seems like between a
12 year and 2 years, you start seeing a difference between an
13 increase in the HBV DNA based upon resistance developed and
14 response. It's that question as to whether you go on for
15 more than a year, but at least a year it seems to me is of
16 benefit in these patients, possibly 2 years.

17 DR. HAMMER: Thank you. I think on that expert
18 note, on behalf of the committee, I'd like to thank the
19 guests and consultants, the sponsor, and the agency for a
20 very interesting day.

21 This session is closed.

22 (Whereupon, at 4:00 p.m., the committee was
23 adjourned.)

24

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1 when the biopsies were done, and in fact we did see a
2 histologic response rate somewhat similar to what Dr. Soon
3 displayed. I have it on a separate slide, but the concept
4 is the same. So, we do see histologic response, as you're
5 indicating, in patients who are still e positive.

6 DR. HOLLINGER: Finally, did you look at any
7 evidence for lactic acidosis at week 52 and particularly at
8 the period of time that's the end of treatment or in the
9 follow-up period when these patients had what looked like
10 flares of their ALT? And also then maybe Dr. Goodman could
11 tell me also whether there's any change in the steatosis
12 levels in the biopsies that he saw at the end of treatment.

13 DR. BROWN: We have a slide on this issue which
14 obviously is, in a sense, an au courant kind of safety
15 issue within the HIV area.

16 It's fair to say we didn't see any of what you
17 might call full-blown cases of the lactic acidosis,
18 steatosis syndrome that's being investigated in HIV
19 patients on combination therapy.

20 Probably the best thing is to go to the slide
21 on this one where I summarize what we found.

22 Another part of the answer is that we didn't
23 systematically monitor blood lactate levels, but instead,
24 these are basically the findings on this issue.

25 First of all, obviously particularly in the

1 transplant patients, but really in any large group of
2 patients as we enrolled in this program, there are a number
3 of things that can be associated with metabolic and lactic
4 acidosis, if you will. And just briefly recounting this,
5 this is actually Harrison's Textbook of Medicine. If Dr.
6 Fauci is here, I apologize if it looks like he's being
7 directly quoted, and there's a misspelling of Braunwald.

8 In any case, so there's a lot of background on
9 this kind of issue that obviously most people in the
10 audience are aware of. Some may not be.

11 We didn't see any cases of the full-blown
12 syndrome in our total development program, including the
13 non-core studies as well. What we did see were two cases
14 of lactic acidosis. One patient was actually asymptomatic.
15 The liver biopsy was normal. The patient did go off
16 treatment, but the reason for the lactic acidosis in this
17 treatment was never really clear. Eventually it cleared.

18 The other patient was a patient obviously with
19 advanced liver disease, cirrhosis, variceal bleeds. And
20 unfortunately, we had minimal information on this patient.
21 A lot of these things are included up here in terms of
22 things that can give you acidosis.

23 We saw six other cases of metabolic acidosis,
24 and the bottom line here is all patients were in the
25 advanced disease, open-label kind of transplant studies, if

1 | you will, and they all had underlying conditions.
2 | Sometimes there was documented sepsis, all the rest of it.

3 | DR. HAMMER: Can you just remind us for the
4 | record of the denominator of all exposed patients in your
5 | program?

6 | DR. BROWN: Well, there's a little bit of
7 | overlap on 1,300 number that Dr. Rubin showed in the
8 | follow-on studies because those are obviously patients that
9 | were studied in phase III and then carried forward. I may
10 | need statistical help on the total denominator there. Not
11 | counting the compassionate use studies. Is that correct?

12 | DR. HAMMER: Can anyone help? Brought out 52
13 | weeks or longer I think to answer Blaine's question.

14 | DR. BROWN: Right.

15 | DR. HAMMER: To put the slide in perspective.
16 | Ball park figure.

17 | DR. BROWN: Yes, I can give you some
18 | approximations. There's approximately 2,500 compassionate
19 | use patients most of whom were advanced disease patients in
20 | the U.S. and Europe. It's hard to say what the median is
21 | at this point, but a good number of them, probably over
22 | half, are on a year, sometimes up to 3 or 4 years, of
23 | treatment. So, that's our compassionate use data which is
24 | being monitored centrally to some extent.

25 | And then in the sponsored program, we have

1 something under 1,900 total patients or so. A fair amount
2 of data at a year or more. Of course, in the HIV arena,
3 thousands, but that's a different issue there.

4 DR. HAMMER: Thank you.

5 Please, Dr. Yogev.

6 DR. YOGEV: Excuse me for reiterating the
7 resistance issue. As much as until now I didn't want to
8 think about HIV, I think this story is reminiscent of what
9 we did with AZT, ddI and so forth. We're checking off to
10 10 to the 5, 10 to the 6, and we claim we know what we're
11 doing and we have much below the curve.

12 What was interesting to me, when you presented
13 data, at 24 weeks the DNA are reappearing in many patient
14 indexes after the same time you start seeing the resistance
15 coming up and going up. To me there must be something
16 connected over there that I don't understand why, if we
17 increase the dose -- and we know that the dose in HIV is
18 higher -- in a virus which is about the same rate to start
19 with, 10 to the 8, 10 to the 10 or whatever, we should not
20 see some data to that.

21 The other question for the FDA. In special
22 populations, for some reason you didn't mention at all
23 pregnant. Are we going to ignore them or this is a
24 population we would like to see some data? Those women had
25 a flare-up of the disease. That's where disease is coming

1 out. I just wonder if any plans or you want to?

2 DR. STYRT: I think it's safe to assume that
3 we're always interested in particular special concerns that
4 might be applicable to pregnant women.

5 DR. JOLSON: And also these are the sorts of
6 issues that if there were no data available now, which I
7 assume that there's probably not, that you all could make a
8 recommendation to the sponsor that they be addressed,
9 presumably as phase IV commitments. Whether it's looking
10 at higher doses, looking at special populations such as
11 safety and efficacy in pregnant women, those sorts of
12 things are all very appropriate recommendations. And I
13 think as you get into the questions, you'll have an
14 opportunity to reiterate some of these issues.

15 DR. YOGEV: And the last quick point. One of
16 the committee asked about the length of the disease for the
17 time that the study started. Did you look into those who
18 were vertically transmitted? Where was your time? It's
19 around the time they were born. So, if we take the age of
20 those patients at the time of the study, we can find out
21 how long they have chronic hepatitis might have any effect
22 on the outcome. Was that done?

23 DR. STYRT: Again, as you've seen in the
24 initial slides, most of the patients -- the most popular
25 reason for acquiring hepatitis B was unknown in these

1 studies. I know that the sponsor has looked at things like
2 age breakdowns and may want to comment on that further.
3 But I think with the largest subgroup of people not
4 necessarily having a known time of acquisition, it could be
5 somewhat difficult to draw conclusions in the current state
6 of affairs.

7 DR. HAMMER: Thank you.

8 I just have two quick questions, another
9 resistance question. Has there been any amplification out
10 of the tissue at 52 weeks to look for YMDD mutants in the
11 tissue that may not be appearing in blood yet and if not,
12 are there plans to do such?

13 DR. BROWN: The first answer is no. It's very
14 difficult to get tissue on multi-center studies, as you can
15 imagine, particularly with a procedure that has a 1 to 3
16 percent serious complication rate.

17 DR. HAMMER: As part of the routine biopsy,
18 PCR, you don't need a whole lot.

19 DR. BROWN: Right. So, it's an excellent
20 scientific question and we've certainly talked about
21 potentially doing some tissue studies. Getting
22 representative samples and appropriate cohorts is a problem
23 when you're trying to get enough information to draw a
24 scientific inference. That can be a problem.

25 DR. HAMMER: I raise it because I think you can

1 sense from the committee and our discussion later will
2 focus a lot on the issue of resistance. So, as much
3 scientific information as can be derived over the next
4 several months to years will be critical.

5 DR. BROWN: Sure.

6 DR. HAMMER: One follow-up question to special
7 populations that were alluded to earlier and briefly
8 mentioned in the packet, and that is, have you teased out
9 the HIV subpopulation in your studies? And can you say
10 anything about response that may or may not be different or
11 the same?

12 DR. BROWN: Right. Patients co-infected with
13 hepatitis delta virus, hepatitis C virus, or HIV were
14 actually excluded from the core phase III trials in order
15 to not have confounded analyses. So, the answer is no. We
16 obviously won't be able to tease out those data from the
17 controlled trials.

18 We do have a little bit of data in HIV/HBV co-
19 infected patients, a retrospective analysis of safety data
20 from the CAESAR study, and then of course a brief
21 encapsulation of the Annals of Internal Medicine
22 publication of Benhamou from November 1996. But we
23 specifically excluded C, delta, and HIV from the core
24 patient population in order to study the effects just on
25 hep B.

1 DR. HAMMER: But even going back to a study
2 like CAESAR, you looked at safety but you didn't look at
3 serial specimens to see what their DNA was doing or
4 anything.

5 DR. BROWN: I think we can say as an
6 exploratory thing we did not look in CAESAR, no. One of
7 the investigators did and there seems to be an antiviral --

8 DR. HAMMER: I raise it because it's one of the
9 questions in part posed to the committee. So, I wanted to
10 give you an opportunity to comment.

11 If there are no additional questions for the
12 sponsor or the FDA --

13 DR. SO: One comment. As a caregiver for many
14 Asian patients, it's encouraging and also interesting to
15 see that from the data presented this morning that the most
16 significant -- the group that showed the most significant
17 improvement is actually the patients in the Asian studies.

18 My question to Greg and Barbara is, do you
19 think it's because that study has the most complete data?
20 Is it because the other studies have so much missing data
21 that it might not show as significant a difference?

22 DR. SOON: Certainly the number of missing are
23 much less in the Asian study. I don't know what's the
24 reason for that, but certainly that helps to make the
25 conclusion more certain.

1 DR. SO: Because traditionally that group of
2 patients is the most difficult to treat because most of
3 them do not respond well to interferon therapy.

4 DR. STYRT: I think there are so many ways in
5 which this study could speculatively be said to have
6 differed from the other studies. Of course, if one of the
7 other studies had been different, we'd probably be coming
8 up with reasons why that study might be different. I think
9 it would be extremely difficult to try to say that there is
10 a definite reason. In fact, as the sponsor has pointed
11 out, it would be rather difficult to say that there is a
12 definite and obvious difference.

13 We felt that there were ways that in the
14 exploratory analyses, this study looked different from the
15 others and that we would be interested in whether it was
16 possible to derive more information that would illuminate
17 that apparent series of distinctions. But I don't think
18 that we can definitely say there is a difference in the way
19 this drug affects different populations from the data that
20 has been presented, only that there are some further
21 questions that we think might be interesting and useful to
22 explore.

23 DR. HAMMER: Dr. Lee?

24 DR. LEE: Actually I'm from Calgary and in
25 response to the question Dr. Hamilton posed, 10 percent of

1 our population is Asian immigrants, a fact which has always
2 amazed me considering that it's way up by the base of the
3 Rockies in Canada and the worldwide perception of Canada is
4 that it's always freezing cold and polar bears roam the
5 streets at will all the time. So, it's amazing that so
6 many Asians settled there. But I do have a fairly large
7 practice of Asians.

8 I think a couple of things that I'd like to
9 comment on, and I think it's clear that there's a major
10 difference in the natural history between Asians and
11 caucasians because one is neonatally or infant-acquired and
12 one is adult-acquired. Clearly these entities differ, and
13 it's not a racial or ethnic thing because Eastern Europeans
14 with neonatally acquired disease behave like the Asian
15 chronic carriers. So, a lot of this data I think can be
16 explained on that basis.

17 The second issue I'd like to raise is actually
18 the issue of the New England where the Claus Niederal paper
19 was published also contained a very thoughtful editorial I
20 think by Ron Coritz which had a number of good points about
21 it. I think he was playing devil's advocate. But here we
22 have a disease that in the majority of people does not
23 cause morbidity or mortality. Somewhere between 15 and 40
24 percent of patients, the minority will get some
25 complication, maybe cirrhosis, maybe cancer, and die from a

1 complication. But if you wait long enough, almost all
2 patients who are chronic carriers in this category will
3 seroconvert into an e antigen negative/e antibody positive
4 form.

5 And the question Coritz asked and I think we
6 should also be asking in a forum like this is, what are we
7 accomplishing with any type of intervention? If the
8 majority of people are going to seroconvert on their own
9 after 1, 2, 5, 20, 30 years, is this therapy going to be
10 useful?

11 I personally think the evidence that has been
12 presented today answers that as yes, but yes, it will be
13 useful to shorten that duration of replicative stage,
14 immune intolerant hepatitis B activity, and hopefully with
15 the logic that it will prevent progression or decrease the
16 rate of progression to cirrhosis in liver cell cancer. So,
17 I think this is an important advance, an important drug.

18 DR. HAMMER: You've answered question 5 already
19 for us.

20 (Laughter.)

21 DR. LEE: Sorry. I didn't realize there was
22 further -- but I have a couple of quick questions and
23 perhaps I'll delay them if this is also going to turn up.

24 DR. HAMMER: I would just say that these are
25 for information for us to discuss later, questions that you

1 have to the sponsor or to the FDA for informational
2 purposes, but we have the next round to expound on our
3 feelings.

4 DR. LEE: Okay.

5 The question to the sponsor or perhaps one or
6 more of the investigators involved in the trials, is
7 eventually when we start using this drug, there's clearly
8 histological nonresponders and e antigen nonresponders.
9 They have suggested the endpoint of using it as waiting for
10 an e antigen seroconversion. Could we get some guidance on
11 the histological nonresponders? When do we stop treatment?

12 DR. BROWN: Let's try M-43. This is a key
13 observation within our program with regard to the factors
14 which may influence histologic response, and in a certain
15 extent, it relates perhaps to Dr. Hamilton's question
16 earlier as well.

17 What we found was the key baseline factor that
18 in a sense interacted with our ability to measure
19 histologic response was in fact baseline Knodell score.
20 The good news is, as patients get more and more severe
21 disease, the numbers get smaller, but the response rates
22 get fairly high. Now, some of these patients may be
23 patients who may be serologically flaring and so may be
24 seroconverting, and the numbers get smaller and smaller.

25 But one of the things that influences one's

1 ability to measure histologic response is baseline Knodell
2 score, and we feel that in patients with quite aggressive
3 disease -- I could show you I guess -- here's another good
4 example. I think hepatologists in the room are used to
5 thinking about cirrhosis as being something that may
6 actually preclude response in some of the previous trials.
7 Here we see the histologic response status by baseline
8 cirrhosis status. In fact, again the numbers of responders
9 are obviously a lot smaller for placebo. Here's the
10 lamivudine group, and what you see is in fact no
11 difference. Cirrhosis does not preclude response to the
12 drug.

13 But I guess your question to some extent is a
14 hypothetical one. In somebody who has no histologic
15 response and no e conversion, I think our data would
16 suggest that is more likely to be somebody who didn't have
17 a lot of histologic disease to begin with. That's a
18 clinical judgment on whether you treat that patient or not
19 in a nutshell because that's likely to be a patient with
20 fairly mild disease.

21 I'm not sure if I answered your whole question.
22 There was another side to it that I probably forgot.

23 DR. HAMMER: Dr. Fletcher.

24 DR. FLETCHER: I know this will be an issue. I
25 suspect it will come up in the discussion, but I would be

1 interested in hearing some response from the sponsor on
2 this issue of the dose difference between lamivudine for
3 HIV and lamivudine for HBV and what you would propose to
4 recommend to a practitioner, to a patient that is co-
5 infected with both viruses.

6 DR. BROWN: Yes. We're certainly recommending
7 that patients who are co-infected get the HIV dose of
8 lamivudine, needless to say, which is the 300 milligrams
9 per day rather than 100.

10 DR. HAMMER: Blaine. This is the last
11 question.

12 DR. HOLLINGER: I was impressed with that.
13 Show that last slide again. Am I interpreting this
14 correctly? Patients who have very bad liver disease at
15 baseline, even the placebo group, have a very large
16 response rate.

17 DR. BROWN: Well, you get a lower number of
18 responders in placebo, but in fact the improvement in
19 patients with what you might call very histologically
20 aggressive disease is easier to measure. But again, the
21 caution here is, as you break down data into subgroups, as
22 is always true, you can get misled sometimes by one's
23 tendency to draw inferences.

24 But, yes, we are saying in a sense patients
25 with pretty aggressive disease or with cirrhosis, in fact,

1 do appear to respond reasonably well. Those don't preclude
2 a histologic response. Somebody who doesn't have a
3 histologic response is most likely to be somebody without
4 much histologic disease to begin with.

5 DR. HAMMER: I'm sorry. I ignored Wafaa. Do
6 you have a question?

7 DR. EL-SADR: I have a question. It seems to
8 me that the population you enrolled in your studies were
9 quite diverse, some with pretty mild disease. Like, for
10 example, in the 309 study, which I think is the study in
11 Asia, the ALT is 1.5 the upper limit of normal.

12 DR. BROWN: Right.

13 DR. EL-SADR: And there are other parameters.
14 They appear to be the least at risk for progression, based
15 on these parameters.

16 As you're thinking down the line of who would
17 be the person to treat, are we here talking about treating
18 everyone in the world who has hepatitis B, who is a
19 carrier, who has any detectable HBV? Because not everyone
20 also got a liver biopsy at baseline. Or are you thinking
21 of a subgroup of patients, and can you define that
22 subgroup?

23 DR. BROWN: Sure. Let me say two things.
24 We're not recommending treatment of healthy carriers. We
25 can say that flat out.

1 The kind of data that was referred to today,
2 the 15 to 40 or the 25 to 40 percent of patients who might
3 get serious disease, that's not predicated on the patient
4 population we've studied. That's predicated on just
5 overall chronically s positive people. The population we
6 studied are patients who previously demonstrated high risk
7 for progressive disease within that chronic surface antigen
8 group, namely patients who are e antigen positive. So, the
9 kind of disease development rates that you heard about are
10 probably higher if you're treating s positive/e positive
11 patients because those are the high viremic patients who
12 are much more likely to get the progressive
13 necroinflammatory liver disease, and those are the kind of
14 patients that we're targeting.

15 It turns out that, when you look at those
16 patients, as we mentioned earlier, even in patients with
17 normal ALT, who are one-third of the Asian study, a fair
18 number of them have histologic disease. In that particular
19 study, we did look at patients with normal ALTs. As I
20 mentioned, their median HAI score was 5. So, in that
21 subgroup within the Asian study who had normal ALTs, there
22 was good evidence that a fair portion of them had some
23 histologically active disease, median HAI score of 5.

24 Now, that's not the same as documenting, as has
25 been done in other studies, someone who is a surface

1 carrier with normal ALTs for 2 years or 5 years or
2 whatever.

3 DR. STANLEY: Sorry. I'll make it quick.

4 DR. HAMMER: Please.

5 DR. STANLEY: But I was struck by that slide
6 also, Dr. Hollinger, but by the number that 73 percent on
7 placebo improved in the most severe disease. Is that
8 telling us that our criteria -- that means they improved 2
9 points on the Knodell scale -- that that's not strict
10 enough or rigid enough to really give us a treatment
11 effect?

12 DR. BROWN: Let me say it was number of
13 responders, but it was the number of placebo responders
14 within that category. The overall number of responders was
15 much smaller for placebo. If you analyze then the
16 subcategories by baseline Knodell, the influence within the
17 small group of placebo patients who responded, the
18 influence of baseline HAI is similar to what you see in
19 lamivudine when you subcategorize them by baseline HAI.
20 I'm not sure if that is what you're referring to, but the
21 overall histologic response rate is what you saw and what
22 Dr. Soon demonstrated as well.

23 DR. HAMMER: I think it illustrates just again
24 the variability in the measurements in this disease over
25 time on an individual basis perhaps and it can influence

1 study interpretation.

2 Dr. Jolson, did you have any comments to the
3 committee before we attack the questions?

4 DR. JOLSON: No.

5 DR. HAMMER: Thank you very much.

6 It's now the job of the committee to respond to
7 questions posed by the agency. What I'd like to do is pose
8 the first question initially and defer the others till
9 after we've discussed this. I'll read it for the record.

10 Does the information presented by the applicant
11 support the safety and effectiveness of lamivudine for
12 treatment of chronic hepatitis B? If the answer is no,
13 what additional studies are needed? If the answer is yes,
14 we will go on to questions 2 to 6.

15 I'll start on my right with Dr. Masur.

16 DR. MASUR: I think clearly the data support
17 the safety in the population that has been studied. Again,
18 there are clearly patients at one extreme of severity where
19 one could desire more control data. But there isn't an
20 issue in my mind about the safety of this data and the
21 doses that they're looking at.

22 In terms of effectiveness, I think there's
23 convincing surrogate marker data that there is an effect
24 for a discrete period of time. There's data that there is
25 clinical -- or there's data at least that there's

1 histologic benefit during that period of time.

2 I guess the concern that has been voiced is how
3 durable this effect is and whether or not it really changes
4 the long-term history of the disease. I think it's very
5 hard to determine from this database whether further out
6 than a year there really is a benefit.

7 Ultimately I think we're all going to wish that
8 there were longer-term data showing that there was
9 histologic and at least enzymatic benefit. Again, the
10 issue about harder clinical endpoints in terms of clinical
11 events and death is very hard to come by.

12 So, I guess overall, given the dearth of useful
13 alternatives, I think that there is enough data to support
14 effectiveness. I'd be willing to support that assertion.
15 However, I'm very concerned that we need a lot more
16 information about how to use this, how to avoid losing the
17 efficacy over time, and exactly when to intervene.

18 DR. HAMMER: Thank you.

19 Dr. El-Sadr?

20 DR. EL-SADR: I agree with Dr. Masur. I think
21 the safety is very clear from the data presented today. I
22 think the sponsor did look at their primary outcome for
23 their study and they did demonstrate the histologic
24 difference between the two arms of the study.

25 I'm very nervous and very concerned about what

1 | it all means and whether in a year or 2 years we'll be sort
2 | of again wondering if we're doing a lot of patients any
3 | favor by maybe this short-term response.

4 | I'm concerned about the dose. I think I'm very
5 | concerned about the dose and whether this is the optimal
6 | dose for treating this infection and especially with the
7 | associated mutants arising on therapy.

8 | Nonetheless, I think that the study did answer
9 | appropriately and positively the primary outcome that was
10 | designed in the study.

11 | DR. HAMMER: Thank you.

12 | Dr. Diaz?

13 | DR. DIAZ: I likewise would agree with the two
14 | prior comments. In particular, the safety is quite readily
15 | available in adults, and it doesn't answer questions for,
16 | for instance, long-term users, but over the period of the
17 | study, I don't have any doubts about the safety of the
18 | drug.

19 | The efficacy, likewise, answered the questions
20 | that really was the histologic endpoints of the study, and
21 | in that regard, certainly I think the proof of efficacy is
22 | there but likewise laud some of the concerns about what
23 | that means overall long-term-wise, what it means in
24 | different groups of patients and likewise the concerns
25 | about having variable serologic and virologic data and what

1 that will mean in the long run.

2 But in terms of the study design, I think the
3 safety and efficacy is there.

4 DR. HAMMER: Thank you.

5 Dr. Hamilton?

6 DR. HAMILTON: To me the sponsors have
7 assembled on an impressive array of clinical trials to
8 support their application for licensure both in terms of
9 efficacy and safety. I too am convinced that safety has
10 been more than adequately addressed and by all means should
11 be continuously followed but would warrant its use on that
12 basis.

13 Having said that, I believe the sponsors have
14 also provided us with ample evidence, given the rules of
15 the game by today's standards, that this agent will, by
16 surrogate marker analyses, alter the course of their
17 subsequent illness.

18 I remain very concerned, however, on a number
19 of points. There's still a lot of virus present. I think
20 Dr. Hollinger pointed that out and others have as well.
21 And increasing amounts of virus apparently in patients on
22 treatment. It's very worrisome to me. And in combination
23 with or in parallel with, these emergent strains of mutants
24 are appearing now even before licensure of this drug. With
25 AZT at least it took a little while until the drug had been

1 given. Now we know it in advance, and the level is very,
2 very concerning to me.

3 Though I'm reassured by the comments of the
4 expert hepatologists in the room that the quality of life,
5 both short-term and longer-term, would be modified by the
6 availability of this drug, there in fact have been no
7 objective measures of that benefit. But I'm satisfied that
8 certainly in making individuals eligible for more
9 aggressive kinds of interventions like transplantation
10 would in itself be useful.

11 Another perspective from which to view the
12 prospects of a given drug I think revolve around its role
13 in the public health. I guess the major focus here today
14 has been on that of the individuals infected to date. I
15 would that to that, however, several other populations that
16 perhaps we haven't thought in as great a detail about, and
17 that would include those who may be uninfected as of now
18 but in positions where they might become infected, i.e.,
19 sexual partners of known infected patients and obviously
20 newborns of infected mothers. I'd be reassured if I knew
21 that such studies actually had already been done or were in
22 the process. I think they're extremely important.
23 Limiting the infectivity of patients could be in and of
24 itself sufficient indication for use of this drug.

25 It's a long-winded way of saying that I believe

1 this drug should be approved but looked at from a variety
2 of other perspectives in subsequent months and years.

3 DR. HAMMER: Thank you.

4 Dr. Yogev.

5 DR. YOGEV: It's always unfortunate to be the
6 sixth in a row to say the same thing.

7 But I think I would agree with my astute
8 colleagues on the committee for adults. I don't think we
9 have near the safety nor efficacy in pediatrics. That
10 should be clearly stated in that recommendation and, in
11 addition, adolescents, although we don't know where to put
12 them. The pediatricians claim they are adult, and the
13 adult claim they are pediatric. So, I think they fall
14 again in between those two, and we don't have data.

15 Also I think it would be very important to
16 suggest -- and I'm again unfortunately reflecting from our
17 bad experience with HIV on those drugs -- that it's going
18 to be for a limited period of time in the majority of
19 patients, and we are going to see a small section of the
20 population which will really enjoy it because we are moving
21 the bell curve probably a little bit to the right. But we
22 need to make sure that it's not taken lightly that it is a
23 wonder drug for everybody.

24 DR. HAMMER: Thank you.

25 Dr. Stanley.

1 DR. STANLEY: Well, I guess that's my biggest
2 concern, is what did we learn from the AZT fiasco, shall I
3 call it, or experience.

4 I'm convinced that, yes, they've shown safety
5 in adults. We don't know enough about the pediatrics, but
6 I'm very concerned about the durability of the
7 effectiveness when we're already seeing in a large number
8 of these patients DNA reoccurring, reappearing, and the
9 resistance developing. So, I'm very concerned that if this
10 is the ideal dose, then it is clearly not able to
11 effectively suppress viral replication to prevent mutants
12 from appearing. And it would suggest to me that we need a
13 multi-pronged approach to this disease, and we may do more
14 harm in the long run to patients by allowing them the
15 opportunity to develop resistance to this single agent.

16 DR. HAMMER: Thank you.

17 Dr. So?

18 DR. SO: I'd also like to echo the same
19 sentiment as the previous speakers. Clearly this seems to
20 be a very safe drug. At least in the short-term it seems
21 to be just as effective as interferon and maybe more so in
22 the Asian population which acquired the disease, most of
23 them, early in life. I think it should be made available
24 for transplantation.

25 But I also am unclear about the long-term

1 sequelae of the development of these YMDD mutants. I hope
2 the sponsors will continue to support long-term studies to
3 see what happens to these patients and whether long-term
4 treatment also will help to decrease the incidence of
5 complications of cirrhosis and hepatocellular carcinoma.

6 I also feel that, yes, we really need more data
7 on the pediatric population before that should be approved
8 for the pediatric patient.

9 DR. HAMMER: Thank you.

10 Dr. Lee?

11 DR. LEE: I thought I didn't get a vote.

12 DR. HAMMER: You can comment. You won't get a
13 vote, but you certainly have full ability to comment as a
14 guest expert.

15 DR. LEE: Well, like Yogi Berra said, just like
16 deja vu all over again. I agree with everything that has
17 been said.

18 I think the situation here can be likened to
19 the company and the community of hepatologists and
20 infectious disease specialists that treat hepatitis B.
21 It's like a 5-year-old kid that has just been given the
22 keys to a brand new Ferarri. He's sort of vaguely aware
23 that he's got something great on his hands. It will take
24 him 20 years to figure out the ins and outs of how it
25 works.

1 DR. HAMMER: Dr. Sjogren.

2 DR. SJOGREN: Well, in thinking and rethinking
3 about the whole issue, I think we could decide to look at
4 the glass half full or half empty.

5 And certainly I echo my colleagues addressing
6 the point of the YMDD mutants, and I think we need to ask
7 the commitment of the sponsor to look a little more into
8 it.

9 Also, the safety and efficacy, although very
10 well established in certain populations, it has not been in
11 some others, and that needs to be brought out, such as my
12 colleague said, the pediatric population, the pregnant
13 population.

14 Also, people that have delta infections have
15 not been studied. Patients that have decompensated
16 cirrhosis, perhaps child's B or child's C, those need to be
17 addressed. I understand the limitations of doing that, but
18 it still needs to be addressed.

19 We must also look at the benefit of the drug in
20 other kinds of mutants. I don't think in the discussion it
21 came out in the morning that the pre-core mutant is
22 something that we deal with as hepatologists all over the
23 world. My reading of the materials, the drug is very good
24 for the pre-core mutants. So, indeed, there is a positive
25 effect in there for some other type of mutations of the

1 virus.

2 I feel satisfied that the safety and
3 effectiveness of the drug is good in the populations that
4 have been studied, but not in the ones that have not been
5 studied for obvious reasons that were explained to us.

6 Also, I want to borrow what I know of e antigen
7 to antibody seroconversion from the interferon trials, and
8 there are hepatologists in the room that can correct me if
9 I'm wrong. But when seroconversion occurs after therapy,
10 it's very sturdy. We have long-term studies in interferon
11 trials, 6, 7, 8 years, a couple of them published in the
12 literature, and when you seroconvert, you are 90 to 96
13 percent likely to remain seroconverted and with normal ALTs
14 7, 8 years down the pike. So, I'm not that familiar with
15 the AZT phenomenon, but I am familiar with interferon and
16 hepatitis B and I know when I see a seroconversion
17 following interferon treatment, I feel very good about it
18 because I know it's going to be a longstanding response.

19 Obviously, the sponsor, as well as the
20 investigators, need to continue to follow up and tell us if
21 this is true for lamivudine or not. My hope is that it is
22 because it is a hepatitis B responding to medication.

23 So, I think although there is some nervousness
24 about it, on the other hand I feel a little bit safer
25 knowing or hoping that it will be a sturdy response.

1 DR. HAMMER: Thank you.

2 Dr. Hollinger.

3 DR. HOLLINGER: I also believe that the
4 information provided by the applicant has supported the
5 safety and efficacy of lamivudine in the treatment of
6 chronic hepatitis B.

7 What we have here is primarily a remission with
8 a small number of patients perhaps engendering a cure, but
9 at least a remission. And the durability of response, as
10 Dr. Sjogren has mentioned, does seem to reasonably good and
11 probably will be long-lasting in most patients. We do have
12 data from Dr. Liaw in Taiwan and others too which have
13 looked at individuals who have gone through a remission.
14 Their survival is improved over ones that do not go through
15 a remission. So, I think we could probably guess that
16 these patients that have a durability of response should
17 have an enhanced survival.

18 In addition, I'm encouraged by the group of
19 patients that do develop the YMDD mutation. It does appear
20 that they have some benefit, and that when the drug is
21 discontinued, most of these individuals will revert back to
22 the wild-type virion. So, I'm encouraged by both of those
23 things. There was a lot of concern that this resistant
24 mutant would make these patients resistant, that they would
25 actually perhaps be worse, but that doesn't seem to be the

1 case.

2 So, I think the applicant has provided support
3 for the safety and efficacy, at least short-term efficacy,
4 of this drug.

5 DR. HAMMER: Thank you.

6 Ms. Melpolder.

7 MS. MELPOLDER: In addition to what everybody
8 else has said, looking at it from a patient's point of
9 view, if I had no other options but lamivudine, I would
10 want lamivudine if it was going to improve my quality of
11 life.

12 The other thing is that when we looked at HIV,
13 we had a drug, and then we found other drugs coming down
14 the pike, and it got faster and faster. And I think that's
15 what we're going to see with the HBV story.

16 So, I would want lamivudine available to me.

17 DR. HAMMER: Thank you.

18 Dr. Fletcher?

19 DR. FLETCHER: I also believe that the sponsor
20 has met the safety criterion and the effectiveness
21 criterion. I think like the other members that have
22 spoken, I have concerns about our ability to offer a set of
23 clear and convincing recommendations to patients, to
24 practitioners about how the drug can then be used in the
25 most effective manner given the heterogeneity and response

1 that has been observed -- not all patients have an initial
2 response -- the durability and the emergence of resistance.

3 DR. HAMMER: Thank you.

4 If it's difficult to be the 6th speaker in
5 line, it's even more difficult to be the 13th, but I'll be
6 brief.

7 I certainly have no questions about the safety
8 profile of this agent as presented and given the broad HIV
9 experience at a substantially higher dose. I share all the
10 concerns that have been mentioned so far, in particular the
11 response rates which we would hope would be better and the
12 durability and the issues of resistance. We don't want to
13 take the analogy to HIV too far, but in fact it's quite
14 helpful here in the sense that we're essentially dealing
15 with surrogates of long-term outcome, whether they be the
16 tissue marker, inflammatory and fibrotic marker evidence,
17 or serologic markers, and we're being asked to look years
18 down the line, knowing that in fact we can't wait
19 necessarily for those trials before approving agents such
20 as these.

21 I think we can also learn that we need to know
22 a lot more about the viral pathogenesis of HBV. We need
23 better assays to do it. We need to learn more about the
24 resistance. For example, given the density of virions and
25 the proposed turnover of HBV, why is resistance taking

1 months to develop? Why isn't it faster in the YMDD region?
2 We don't know the answer to that and some very interesting
3 possibilities may emerge. I think as we get more sensitive
4 assays, maybe in fact it will be a high proportion early,
5 but if it's not, then we'll be learning something very
6 important about this disease.

7 It has been said many times -- and it's clear
8 -- we need standardization and better assays. Again, it's
9 a viral disease. When we can measure it accurately, then
10 some of the other surrogates of immunologic antibody
11 development may be less important than persistent hepatitis
12 B virus suppression.

13 So, lastly I think we have to be concerned
14 about what we learned about monotherapy, particularly drugs
15 that can develop resistance in treating HIV with
16 nucleosides, but we can also learn from that and move very
17 quickly into trials and experiments and studies that teach
18 us something and move faster and learn from the past. So,
19 immediate moving into combination trials, for example, is
20 clearly the way to go.

21 So, I also think that the efficacy has been
22 shown in the trials to date. The primary endpoint was
23 histologic improvement. It was clearly met in three
24 studies with very consistent results, and we all have the
25 same questions which we'll spend the next hour or more

1 trying to discuss.

2 So, we now move to the vote before we discuss
3 the other questions. The voting members present are just a
4 few actually: Drs. Diaz, Hamilton, El-Sadr, Masur,
5 Hollinger, and me.

6 I would restate the question for the record.
7 Does the information presented by the applicant support the
8 safety and effectiveness of lamivudine for treatment of
9 chronic hepatitis B? The voting members, if your answer to
10 this question is yes, please raise your hand.

11 (A show of hands.)

12 DR. HAMMER: It's unanimous obviously.

13 So, now we are asked to move on to questions 2
14 to 6, and I must say that this is the longest and most
15 dense list that we've seen in a while. A lot of these
16 issues have been addressed and many of them are
17 intercalated. So, for the record and the people in the
18 audience, I'm going to read questions 2 through 6. I'm
19 then going to ask the panel members to take some time and
20 really try to address the aspects of these that each one
21 feels comfortable with and try to present some cohesive
22 suggestions to the sponsor and the agency.

23 The questions that we're now being asked to
24 deal with are the following. What post-marketing
25 information is desirable to determine optimal use in

1 patients with compensated chronic hepatitis B disease, such
2 as those included in the principal phase III trials, and in
3 other populations such as pediatric patients or patients
4 with decompensated liver disease?

5 Next, how should the following events influence
6 decisions to stop or continue therapy: e antigen
7 seroconversion, development of viral resistance,
8 reappearance of viral DNA during therapy?

9 How should patients be monitored for safety and
10 effectiveness during and after therapy?

11 How can the optimal treatment duration for
12 specific patient groups be defined?

13 Next, question. Please discuss the
14 implications of viral resistance development for long-term
15 use of lamivudine monotherapy. What recommendations can be
16 made for future development of combination therapy?

17 Next. To what extent can virologic and
18 serologic results be used as a proxy for histologic
19 changes? Please discuss the relationship between either
20 virologic/serologic or histologic changes and long-term
21 outcomes such as cirrhosis and hepatocellular carcinoma,
22 and how such relationships can be confirmed.

23 And lastly, what information should be made
24 available to physicians and patients concerning potential
25 effects of lamivudine treatment for hepatitis B on

1 unrecognized or untreated HIV infection? What are your
2 recommendations regarding ascertainment of HIV status for
3 treatment of hepatitis B with lamivudine to avoid
4 inadvertent use of a single nucleoside analog in an HIV-
5 positive patient?

6 I think the last one is somewhat rhetorical but
7 the easiest to answer.

8 I would like to start on my left with our
9 guests and consultants. Dr. Fletcher, would you like to
10 address these in sequence or whatever you feel comfortable
11 answering within the span of a reasonable -- before
12 midnight.

13 (Laughter.)

14 DR. FLETCHER: Thank you for clarifying that.

15 I guess maybe I'll start with number 2 and the
16 optimal dose issue. I think it has arisen in the comments
17 of several individuals whether we have the optimal dose.

18 As I mentioned in an earlier question, I think
19 the pharmacodynamic modeling for the short term are very
20 convincing about a plateau effect once doses above 100
21 milligrams are reached. But the pivotal studies went for
22 longer than 6 months out to 1 year, and it's there that we
23 saw the loss of response and emergence of resistance. And
24 I think a natural question has to arise as to whether we
25 really have an optimal dose or not. So, I think data that

1 I and probably others would like to see is does the use of
2 larger doses affect the proportion of patients that achieve
3 a response, duration of response, and the emergence of
4 resistance.

5 With regard to the pediatric patients, I think
6 the pharmacokinetic information that are provided in the
7 packet indicate that the proposed dose scales very well in
8 terms of pharmacokinetic equivalence between pediatrics and
9 adults, but I don't believe that we could rely just on
10 pharmacokinetic information, that if you achieve
11 equivalence there, you will then have an equivalent effect.
12 So, longer-term studies of children I think clearly need to
13 be done.

14 I think maybe the next issue that I would
15 probably want to jump down to is related to question 6, and
16 that is the issue of the co-infected patient with hepatitis
17 B and with HIV. While I think the recommendation in that
18 case to use the 300 milligram daily dose for HIV is very
19 reasonable, it does pose some unknowns in that the safety
20 of the drug for hepatitis B is for a lower dose. The
21 effectiveness was for a lower dose, and is there something
22 disease-related that could affect at least safety when
23 using a higher dose?

24 But it's also the issue of I guess the addition
25 of lamivudine for treatment of hepatitis B in patients that

1 are not receiving that drug for the treatment of HIV, and
2 does that additional nucleoside, most likely on top of
3 additional nucleoside therapy, then pose any safety or
4 efficacy concerns? I think the practical recommendations
5 on how to deal with that I think remain a real unknown, at
6 least unknown, not clear in my mind.

7 I think at least for right now, Scott, I'll
8 stop.

9 DR. HAMMER: Thank you.

10 Ms. Melpolder, do you have comments?

11 MS. MELPOLDER: I think I would use lamivudine
12 judiciously. I wouldn't use it unless there was a reason
13 to use it. I would be concerned about the resistance to
14 the drug and consequently that would be something that I
15 would take in consideration if I were going to use the drug
16 on an HBV positive person.

17 As far as the HIV, it seems to me that you
18 would have to determine the HIV status so that you wouldn't
19 do harm to the patient by putting them on lamivudine.

20 I'm not sure what you could use to determine
21 when to stop drug or whether to continue drug. I guess
22 since we know that the e antigen seroconversion seems to be
23 fairly durable and the viral resistance seems to be to me
24 the big stickler, I would go on viral resistance.

25 DR. HAMMER: Dr. Hollinger? Thank you.

1 DR. HOLLINGER: It's hard to pick which one to
2 talk about.

3 Just a couple of things. I think the patient
4 with decompensated liver disease I think is a really
5 critical group, and those of us who have taken care of
6 patients who look like they're really doing very poorly and
7 have treated them with lamivudine and seen a relatively
8 good response in these individuals have been very
9 encouraged with the possibility that this could be a bridge
10 at least to liver transplant for the short term. I think
11 those issues are going to be most helpful, as well as the
12 issue about the use of lamivudine in the transplant arena
13 since it would be considerably less expensive than the use
14 of hepatitis B immune globulin. So, I think that's an area
15 that clearly needs to be evaluated.

16 The question of number 5 about to what extent
17 can virologic and serologic results be used as a proxy for
18 histologic changes is really an important one. In
19 hepatitis C it was really fairly easy. I think we all,
20 after a while, came down to the fact that we really don't
21 need liver biopsies. I know the FDA always wants to have
22 liver biopsies, and I think we've tried to argue with them
23 many times that, look, you don't need it for this disease.
24 There is plenty of data out there that suggest that looking
25 for normalization of the ALT and a reduction in HCV RNA is

1 sufficient, that the correlation is excellent.

2 I'm not sure I've heard that yet with this
3 data, but I'm not sure that I really have the data to look
4 at it. There was some information that the FDA presented
5 which suggested that if they met criteria, they met the
6 seroconversion criteria, that you were very likely to find
7 histologic improvement.

8 On the other hand, there was a fairly large
9 group of patients that did not meet the seroconversion
10 criteria, and because it wasn't put in there, I don't know
11 if they meant both HBV DNA, the absence by the test that is
12 used, and normalization of the enzymes, or one or the
13 other, or both.

14 Then there was a fair number of them that had
15 histologic improvement despite the fact they did not meet
16 the seroconversion criteria. But I don't know again if
17 histologic improvement there met fibrosis or a change in
18 necroinflammatory activity. I might look more favorably if
19 it meant fibrosis than I would if it was necroinflammatory
20 activity.

21 So, that kind of data is probably there. I
22 guess just haven't either seen it or wasn't aware of it.
23 It may have been in the booklet here. I thought I looked
24 through most of that, but I could have actually missed that
25 data.

1 But I do think that's really critical because
2 it is hard to get patients to agree to another liver biopsy
3 12 months later, and that is often required or asked by the
4 FDA. I have to be honest. I really disagree with that
5 requirement. Certainly you need a baseline to know where
6 you're starting from, and I would probably feel reasonably
7 good if a patient showed a remission in their disease by an
8 absence of their HBV DNA and a normalization of ALT. This
9 will probably correlate very well with the histologic
10 change. But I would like to see and hope to see perhaps
11 they could provide more information regarding what these
12 changes mean and where there's a better correlation either
13 with the HBV DNA or with the ALT and these histologic
14 changes. So, I think that's something that needs to be
15 looked at more carefully.

16 DR. HAMMER: Thank you.

17 Dr. Sjogren.

18 DR. SJOGREN: I think that the information that
19 I would like to see, after marketing is approved, is that
20 they tell us what are the serious adverse events that
21 continue to be observed in these patients. Obviously, I
22 would like to know what is the duration of the e antigen
23 seroconversion, and by and large, I would like to know
24 everything there is to know with the long-term follow-up of
25 the patients that were treated in the registration trials.

1 As I said before, decompensated liver disease
2 is a must. We need to make some attempts to look at those
3 patients even if they are not well-controlled.

4 With fear and trepidation, I must disagree with
5 Dr. Hollinger, one of my mentors and beloved friend.

6 (Laughter.)

7 DR. HOLLINGER: Go ahead. Stick it.

8 (Laughter.)

9 DR. SJOGREN: And on my knees --

10 (Laughter.)

11 DR. HAMMER: You just have to change seats.

12 DR. SJOGREN: I would say that were it not for
13 liver biopsy in the studies that we have just seen, we
14 would be totally confused. Indeed, it is the histological
15 improvement that was shown by the registration trials which
16 has swayed my mind and maybe some other people's minds
17 because that's really where it's at. We want to see people
18 that have a histological response. Particularly now they
19 will learn that the e antigen seroconversion and the DNA
20 maybe is not all what we hoped it to be.

21 With one request to the sponsor -- and this is
22 borrowed from the experiences with hepatitis C -- that they
23 don't biopsy at the end of treatment, but that they biopsy
24 at the end of follow-up so we can look at the effect of the
25 drug away from the last day it was given or the patient

1 might have taken the drug that week and be biopsied and
2 there's always the speculation whether you're still under
3 that kind of influence. So, in hepatitis C we have moved
4 away now. 6 months after stopping the drug or 3 months
5 after stopping the drug, that's when we biopsy and see
6 whether there is an effect or not.

7 So, I would plead for continuing with liver
8 biopsies. I do them myself. I know how hard it is. I
9 have to convince patients. And it is much easier to do a
10 blood test, but I think in terms of understanding what
11 we're doing, we still need to continue doing that test.

12 Certainly I am very curious and want to know
13 what happens with the combination of interferon and
14 lamivudine, and I think that's a must, that those studies
15 need to be done again with a sufficient number and a clear
16 design that could answer the questions. Obviously not
17 every patient can go on interferon and lamivudine. They're
18 both powerful drugs and they have to be patients that can
19 tolerate both. But I think for what was presented to us, I
20 could see a ray of hope. I could see light at the end of
21 the tunnel, and I would like to pursue it and know that I
22 can offer that to my patients.

23 The HIV question. Obviously patients need to
24 be tested before treatment, but then how often? That's a
25 very serious question, especially in risky populations. In

1 the military, we are tested every year whether we want it
2 or not, so we know our status of HIV or hepatitis. You
3 name it, we know it. We know even our DNA. I'm told we
4 have no constitutional rights.

5 (Laughter.)

6 DR. SJOGREN: So, in our population it's a
7 must.

8 But what about the clinics where that is not a
9 must? Maybe testing every 6 months, every 12 months, I
10 don't know because I don't deal in that world. Certainly
11 when we deal with IND drugs and we face possible pregnancy,
12 we test every month. I don't know in HIV. I think I would
13 have to defer to my colleagues that deal in that arena in
14 alerting us and the public what is best in terms of HIV
15 testing, but it worries me that some people could get
16 monotherapy with the obvious complications of it.

17 I am disappointed in terms of the lack of
18 histologic changes and serology results. I mean, it's
19 dogma. When I was trained in hepatology, it was dogma to
20 us that they went hand in hand, and I think the importance
21 of these studies, that the textbooks have to be rewritten
22 now. There's no such thing and we have to just face it.
23 It's not the fault of Glaxo or lamivudine. It is just the
24 way it is and we just need to be alert to that.

25 So, again my plea for liver biopsies in these

1 patients. Thank you.

2 DR. HAMMER: Thank you.

3 Dr. Lee.

4 DR. LEE: I guess I've already shot my load on
5 a couple of questions before. But I just want to touch on
6 a couple of points.

7 The patient with decompensated liver disease.
8 I think we all have one or two or a few cases of patients
9 who are on a transplant waiting list and were treated with
10 lamivudine and had a dramatic response. In fact, there is
11 a Canadian abstract that looked at it. I think this is the
12 kind of very encouraging and significant -- these patients
13 often have no other therapeutic recourse at all, and this
14 is a very encouraging development, that some of them
15 improve dramatically to the extent that they come off the
16 transplant list altogether. I've had a patient go from a
17 Child-Pugh C to an A on nucleoside analog treatment. So, I
18 think this is an area that really bears further
19 investigation.

20 Question 3 about all sorts of questions about
21 when we stop or continue therapy. Well, gee, I wish we had
22 some answers. It would make sense to me that when someone
23 has an e antigen seroconversion with development of anti-e,
24 that that would be a reasonable time to think about
25 stopping.

1 As for the other questions about resistance or
2 reappearance of DNA during treatment, I don't know. I
3 guess we'll just have to wait a few years for those answers
4 to come out.

5 I have a little note here just about this
6 decompensated disease. I would like to interject a plea of
7 caution in that I've just recently lost a patient. It
8 wasn't this drug. I've treated with a nucleoside analog a
9 patient with cirrhosis, fairly advanced, just because we
10 had no other options, and he was replicating. Our
11 transplant program won't transplant replicating B patients.

12 After giving him a nucleoside analog for 6
13 months, it was e antigen still positive, DNA still
14 positive. I stopped the drug, also at his request because
15 it was costing a fortune. The patient decompensated very
16 dramatically within 2 to 3 weeks of stopping the drug, went
17 into a very progressive liver failure with eventual
18 hepatorenal syndrome and died.

19 I think this points out that with any new drug
20 or technology, that we really need to be very careful. I
21 would suggest that clinicians don't go about willy-nilly
22 just giving people with decompensated disease these
23 nucleoside analogs, or if they do, that they consider that
24 this is probably going to be indefinite treatment in this
25 special group.

1 Again, I'd like to echo Dr. Sjogren's comments
2 about the plea for development of combination therapy. I
3 really think that is the future, despite what the data from
4 the 3010B study showed with the active control, not just
5 combinations of interferon and lamivudine. We know that
6 other nucleoside analogs develop mutations at different
7 sites, and perhaps the key to overcoming the YMDD mutant is
8 to give those patients another nucleoside analog that
9 develops a mutation at a different site, analogous to the
10 fashion that HIV is currently treated.

11 I'm Canadian, so we're expert at sitting on
12 fences and not taking a firm stand. So, I'm going to sit
13 on the fence equidistant between Drs. Hollinger and Sjogren
14 in terms of liver biopsy. I think they're indispensable in
15 clinical studies, especially these registration studies.
16 But in clinical practice, I don't really think they're
17 necessary for the vast majority of patients. Certainly
18 trying to get many of my patients, almost all of whom are
19 Asian, to agree to a first, let alone a second biopsy is
20 virtually impossible, akin to trying to get the American
21 media to stop reporting the Clinton/Lewinsky scandal. It's
22 okay. I'm Canadian, so I guess I'm allowed to say that.

23 DR. HAMMER: We were going to try to avoid
24 getting that into the transcript.

25 (Laughter.)

1 DR. LEE: Unfortunately, this question that
2 you've posed about the relationship between the virologic
3 or serologic data and the histology in the long-term
4 outcome such as cancer and cirrhosis are, unfortunately,
5 because so many drugs are coming about on the scene, not
6 just interferon, but this drug and others due to appear
7 shortly, I don't think long-term studies are going to be
8 possible. This is unfortunate, but it's going to be hard
9 to find a cohort of untreated controls to see the natural
10 history and the effect of these analogs.

11 Anyway, I think I've said enough.

12 DR. HAMMER: Thank you.

13 Dr. So?

14 DR. SO: I think the previous speakers covered
15 pretty much all of the stuff I'm going to address.

16 As a transplanter, I also would be interested
17 in having the sponsor have studies addressing whether
18 lamivudine helped to down-stage patients waiting for a
19 liver transplant. We probably all have some anecdotal
20 cases where a patient was listed for emergent transplant
21 and, with lamivudine treatment, they stabilized and was
22 discharged from the hospital without having to undergo
23 emergent transplant.

24 But on the other hand, I'm also concerned about
25 the emergence of YMDD mutants in patients pre-transplant,

1 and we should restudy whether that would affect the
2 recurrence rate after transplantation.

3 Also, as a person who also performs liver
4 resections, it's well known that after liver resection in
5 patients with chronic hepatitis B, the 3-year recurrence
6 rate even for small tumors is as high as 70 to 100 percent.
7 So, it will be interesting to see whether treatment of
8 these patients after liver resection can help to reduce the
9 recurrence rate.

10 Also, as a children's advocate, I think it's
11 very important to study the long-term treatment effect in
12 the pediatric population.

13 As far as the treatment endpoint, it would be
14 simple to adopt HBe antigen seroconversion as a treatment
15 endpoint, but once again, I'm not sure whether that really
16 is adequate, and I would hope there would be long-term
17 studies to address whether long-term lamivudine use, as
18 long as the patient has suppressed HBV DNA and
19 normalization or near normalization of ALT, helps to
20 decrease the long-term sequelae of the infection.

21 Lastly I want to just make a few comments about
22 what I'd like to see in terms of combination therapy.
23 Definitely we should think about combination lamivudine
24 therapy with other nucleosides or nucleotide analogs to see
25 whether that would decrease the incidence of recurrence of

1 mutant development.

2 Also, since lamivudine only suppressed the
3 viral DNA and doesn't get into the hepatocytes which in
4 fact live inside the infected liver cells, once again I'd
5 like to echo my previous colleagues that we should, once
6 again, do a good study with lamivudine with interferon or
7 other newer modes of therapy which cause apoptosis of these
8 HBV infected hepatocytes.

9 Thank you.

10 DR. HAMMER: Thank you very much.

11 Dr. Stanley.

12 DR. STANLEY: I'll go to number 6 first.

13 As far as testing to recognize HIV infection,
14 my knee-jerk reaction is to say that it would be required
15 because it's unfortunately still all too common for people
16 to stereotypify the risks for HIV and to underestimate
17 their own or their patients' risks for HIV. So, I would
18 tend to be more bold and say that testing should be
19 required, but there may be modifications we can make on
20 that.

21 The other thing, in regards to the co-infected
22 patient, is not only should the clinician be instructed to
23 use the higher dose, but should be aware that in the
24 patient who is not requiring treatment for his HIV yet, a
25 commitment to use lamivudine for his hepatitis B really

1 probably commits that patient to the full triple drug
2 therapy for HIV which is the standard now, so that it's a
3 more complex decision. I don't know how many hepatologists
4 would be educated enough in that since many infectious
5 disease and internal medicine docs aren't educated enough
6 in that yet. So, that would be an area where consultation
7 might be required.

8 With regard to question 2, again I think we
9 need a commitment from the sponsor for some long-term
10 follow-up of these patients to see what the outcome is. I
11 hate to take the analogy and the experience too far, but I
12 don't want to see 3-year Concord follow-up come out here
13 and we find out that our monotherapy has not done a good
14 job. So, I think we need a commitment there.

15 Certainly still I have questions about the dose
16 appropriateness.

17 I think that we need a sponsor, to echo other
18 comments, for looking at combination therapies with not
19 just interferon but other nucleosides.

20 Finally, with regard to question 3, I agree
21 that e antigen seroconversion is probably a good time to
22 start thinking about stopping therapy. If we can learn
23 anything, though, from our HIV experience, reappearance of
24 viral DNA or viral RNA in the case of HIV on triple therapy
25 has been used as a trigger point to consider changing

1 therapy, but yet anecdotally people are still seeing good
2 clinical responses despite what we call a virologic
3 relapse. So, I'm not sure that reappearance of viral DNA
4 in hepatitis would be a reason to stop therapy. I don't
5 know if we can compare those two experiences, but I just
6 throw that out as a thought.

7 I think that's all I'll say.

8 DR. HAMMER: Thank you.

9 Dr. Yogev.

10 DR. YOGEV: Well, first, I think the major
11 problem we didn't address is what happens to the patients
12 after you stop therapy. I was quite impressed with the
13 number of patients who had liver enzyme elevation when you
14 stopped it. There are already two reports in the
15 literature about liver failure following lamivudine, and we
16 also have to be very careful because there's one case
17 reported, at least that I'm aware of, of a combination of
18 lamivudine and stavudine that on therapy caused liver
19 failure. So, I think this issue of the effect post-therapy
20 has to be followed very closely.

21 I would like to see the drug really being
22 limited to the most severe cases because of the shortness
23 of disease, before transplant, for example. It's an
24 excellent example.

25 I hope that the agency somehow will hold the

1 company unlimited time for adult to make sure that the
2 pediatric, the pregnant women will be also part of the
3 studies so we know what to do with them. As far as I'm
4 concerned, 6 months of positive antigen is chronic disease.
5 Every newborn who got the infection for 6 months is chronic
6 of this disease and we need to work it out.

7 We didn't talk at all about compliance. I
8 think that's a major issue. Being an HIV person, for many
9 years I believe it's a virus and I think the reason why I
10 believe in that is because we did not yet affect the immune
11 system enough with reduction of the virus, and what we're
12 seeing over here is probably a limited effect on the virus
13 which we don't see because of diagnostic tests which we
14 need to develop. That's why the immune system which we try
15 to follow is not as good.

16 Therefore, to avoid liver biopsies, I think we
17 need to look into the virus itself, and when we see it's
18 coming up, that should be a point to the physician to start
19 investigating compliance versus efficacy of the drug.
20 According to the liver status at that time, I would stop
21 and start because I don't think there is a major problem
22 stopping because we were told amply that the wild virus is
23 coming back. So, we can correlate now what happened to the
24 liver at that point in time and then stop. So, we have
25 some parameters how to decide the more aggressive disease

1 to approach and when to stop and start with the limited
2 weapons we have.

3 As for the HIV testing, I think if we start
4 treating because it's 1-point mutation for HIV and that's
5 it, that maybe some recommendation to discussion with the
6 patient that as we test the liver enzyme or whatever once a
7 month or whatever, we should then test for the HIV to catch
8 if the unfortunate patient got the HIV infection, that we
9 catch it early enough to not have a longer period of time
10 on monotherapy and we know what happens.

11 As for combination therapy, I think we have to
12 insist on doing it because I think the handwriting is on
13 the wall. All of us are seeing it. Just because we are
14 desperate, I think this drug should be approved but, as I
15 said, to a limited population.

16 DR. HAMMER: Thank you.

17 Dr. Hamilton?

18 DR. HAMILTON: I would like to see the
19 committee lay the mantle of responsibility directly at the
20 feet of the sponsor to perform all of the following
21 concrete ideas, my ideas.

22 (Laughter.)

23 DR. HAMILTON: First of all, I think it's very
24 important that the sponsor emphasize the proper patient for
25 whom this drug is indicated. To extrapolate beyond the

1 experimental evidence would seem to me to be a shame and
2 asking for trouble in all kinds of ways, many of which you
3 wouldn't want.

4 Secondly, I think the sponsor should assist in
5 the development of a more sensitive test for this virus,
6 one which would give us substantially greater confidence
7 that we are doing something beyond simply suppressing.

8 Third, I think the sponsor is in a position, an
9 ideal position I think, to provide us with ongoing evidence
10 of the rate at which emerging resistant viral strains are
11 occurring. The trials are in one sense over, in another
12 sense not, and I believe some extremely valuable
13 information can be obtained there. And I believe the
14 sponsor could assist in the establishment of standards,
15 arbitrary as they may be at this moment based on incomplete
16 information, to define failure of therapy. I don't think
17 we can divine what that is at this moment. We need to find
18 out and test the hypotheses.

19 To that end, I think you could set up a
20 clinical registry, including all of the patients that
21 you've enrolled to date, and test hypotheses that are
22 generated in the course of the various deliberations that
23 have gone on here today and in your own offices.

24 There are some subsets of patients who I think
25 should be studied in substantially greater detail. I've

1 already mentioned that I thought the pregnant woman and her
2 newborn are critical. It certainly has proven to be the
3 case with HIV.

4 I'll echo the recommendation that combination
5 therapy using non-nucleoside, other classes of drugs will
6 inevitably become essential. What those are I wouldn't
7 know at this point, but it should be explored.

8 Lastly, I'd like to make an appeal for this
9 drug to be more affordable to the individuals who will
10 ultimately use it. I don't know the impact which this
11 committee has on those kinds of decisions, but I can tell
12 you that it's a very, very real element in both the
13 decision to treat, to extend therapy, and we're talking
14 here about treatments that may be lifelong. Who knows.

15 Those are my recommendations.

16 DR. HAMMER: Thank you.

17 Dr. Diaz?

18 DR. DIAZ: Thank you.

19 I'd like to just address a couple of the
20 questions, in particular question number 2 about post-
21 marketing information. I'm still struggling with trying to
22 answer the question when would it be best to start therapy
23 in addition to questions about when would one stop therapy.
24 I certainly agree it's a drug not to be lightly taken and
25 certainly not for all patients. Yet, there is this

1 interesting data in the Asian population that we've
2 struggled with today a little bit about is there something
3 unusual about that population perhaps that lend it to
4 better outcome in terms of at least less resistance and
5 sustainability. One of the important criteria that was
6 alluded to was that in this particular study, likewise the
7 Asian population was perhaps less progressed in their
8 disease at the time of entry.

9 So, it does bring up some interesting questions
10 about when might one want to start therapy, and in
11 particular I think we need some predictors of a response to
12 therapy. If we could in some way be able to better
13 identify patients who would respond to therapy before we
14 even start, we might have a better ability to choose the
15 patients that should be treated with this drug.

16 I think the dosage of the drug has been dealt
17 with by multiple individuals and I won't go into that any
18 further.

19 Certainly how long to treat or perhaps when and
20 how to retreat an individual is an extremely important
21 question to answer.

22 Likewise, should one continue to treat despite
23 perhaps the reemergence of detectable HBV levels?

24 As far as the decision when to stop therapy, I
25 have even more difficulty grappling with that question. In

1 terms of e antigen seroconversion, in order to sort of
2 answer that question in my mind, I think it's important to
3 know what the durability is off therapy, and I'm not sure
4 we have the answer to that particular question. So,
5 although e antigen seroconversion is perhaps a good marker
6 for considering stopping therapy, I think we need more
7 information to know what the durability is off therapy in
8 order to use that as a decision point.

9 Likewise, in terms of developing viral
10 resistance, it's another issue to deal with that I would
11 not want to address at this point, but more so tackle the
12 issue about reappearance of viral DNA. Many individuals in
13 the study did have reappearance of viral DNA. And yet I
14 think it's important for some criteria to be set as to how
15 many times one might be tested, over what period of time in
16 order to assure that viral DNA has reemerged, and if so, is
17 that a criterion for stoppage of therapy? I'm not sure.
18 It seems in some of the data that was presented in those
19 individuals who had reemergence of viral DNA, only about
20 half of those patients had YMDD mutants detected. So,
21 again I think we need more information about long-term
22 reemergence of viral DNA perhaps and over what period of
23 time before we use that as a solid criteria for stoppage of
24 therapy.

25 The last couple of comments that I think I

1 would make would be to address the fifth and sixth
2 question, the fifth question in particular, to what extent
3 can virologic and serologic results be used as a proxy for
4 histologic changes? I think it's an important question to
5 try and answer because we've heard different opinions today
6 about the use of liver biopsies or at least the willingness
7 to do liver biopsies. I think we need to continue the
8 recommendations to follow liver biopsies because I don't
9 think we'll answer a lot of the questions without having
10 that and organ response to compare to.

11 And in particular for virologic, I was looking
12 at the FDA's table that they put together, table 7, in
13 trying to sort out that question as far as virologic
14 response to be used as a proxy for histologic change. It
15 seemed to me that with those individuals who were
16 persistently suppressed, there was a fairly decent
17 correlation or at least a higher percentage of histologic
18 responders, but if there was reemergence of viral DNA in
19 particular, there was some decrease in histologic response.
20 And perhaps further elucidating those individuals, coupling
21 their reemergence with perhaps the development of mutants,
22 that type of data might further sort out those individuals
23 in terms of the reliability of virologic response as a
24 marker for the histologic response.

25 For those individuals who had late suppression,

1 | though, I'm not sure if we followed them out far enough to
2 | really be able to tell if one could then go on to use their
3 | data to support the histologic response pattern. Certainly
4 | in those individuals who were unsuppressed, they seemed in
5 | my mind not to be much different in terms of their scores
6 | than those individuals on placebo.

7 | So, I think there's perhaps some validity in
8 | looking at virologic response and coupling it with
9 | histologic response, but I think we need to continue to
10 | monitor and do further studies looking and correlating it
11 | with liver biopsies. And if we stop doing that, we won't
12 | get the answer to those questions.

13 | Finally, in special patients in particular, I
14 | would very much want to see data in pregnant women in
15 | particular because 5 percent or so of perinatally acquired
16 | HBV occurs in newborns who are born to HB surface antigen
17 | positive moms where the baby has received HBIG and vaccine
18 | appropriately at birth. So, there's a small percentage of
19 | babies who, despite the use of good preventive
20 | intervention, will go on to be chronic carriers. So, I
21 | very much would like to see information coming out in the
22 | future on pregnant women.

23 | As far as the pediatric population in
24 | particular, I think the question when to use this in the
25 | pediatric population is an extremely important question to

1 answer, how long to treat pediatric patients. I don't
2 think we have the answer to any of these questions
3 obviously. And when might we use it and get the best long-
4 term effect without sort of playing all our cards at too
5 early a time in these young individuals' lives?

6 More importantly, how could we best avoid
7 mutations and perhaps what might the effect of puberty on
8 the disease progression and likewise interactions with
9 treatment?

10 There are other individuals, special groups,
11 that could be mentioned such as transplant patients. In
12 particular, I think we might be able to get data on
13 hepatocellular carcinoma development, get that question
14 answered more quickly in those patients than in other
15 patients.

16 Also, I would like to see some information on
17 patients who are on immunosuppressants like prednisone and
18 other immunosuppressants and their effect on therapy.

19 I should stop.

20 DR. HAMMER: Thank you.

21 Dr. El-Sadr.

22 DR. EL-SADR: I do think that this drug
23 provides a wonderful opportunity for the sponsor, in
24 conjunction with others, to really try to answer some very
25 key questions about this virus and its treatment. Probably

1 it's going to require continuing to do more and more
2 studies because we've learned a whole lot from this study,
3 but I think it's opened a whole lot of other questions that
4 are key to managing chronic hepatitis B infection.

5 I guess in my own thinking, it's hard for me to
6 imagine stopping treatment for this infection with the
7 available agent, with this antiviral, because even when we
8 use the term e antigen seroconversion, it's really a
9 misnomer. It's not seroconversion. We do know that
10 there's a lot of virus there. It's just that our assays
11 are not really very good. So, even at best with
12 seroconversion, there is evidence there's a whole lot of
13 virus in these patients and probably it's going to be
14 unlikely that we're going to be able to cure the infection
15 with the available agent, at least in a substantial number
16 of the patients.

17 I think, on the other hand, the opportunity to
18 study interferon alfa and lamivudine is a wonderful
19 opportunity with an immune modulator and an antiviral drug.
20 With a nicely design study, we probably could learn an
21 awful lot and maximize the response to this combination
22 treatment. I do believe that it's a combination treatment
23 that's going to ultimately make a difference in the outcome
24 for these patients.

25 The issue of histology versus serology. Again,

1 with the state of the art of the situation with the
2 serologic tests, I think we have no choice but to continue
3 to seek better serologic tests that are always in
4 conjunction with the histology. So, I think we're really
5 compelled to continue to use the liver biopsies to look at
6 what happens in the individual patients.

7 I'm concerned about the issue of the mutants.
8 Although it's reassuring that the wild-type virus does come
9 back after stopping treatment with lamivudine, it's unclear
10 whether retreatment with this drug will be as effective as
11 the initial treatment with lamivudine. So, that also may
12 need to be looked at as well.

13 Finally, the issue of the HIV infected, I think
14 both HBV and HIV are sexually transmitted as well as
15 transmitted parenterally. So, clearly the population at
16 risk for one is at risk for the other, and it would be wise
17 to strongly recommend HIV counseling and testing for
18 patients who do have hepatitis B infection in general, but
19 even more importantly for people who are going to go on
20 monotherapy with lamivudine.

21 I think there are some populations where I
22 think this drug offers great opportunity like the
23 transplant patients to prevent infection of the
24 transplanted liver, and a few of the other populations that
25 have been mentioned so far.

1 DR. HAMMER: Dr. Masur.

2 DR. MASUR: Most of the major points about the
3 opportunities and problems have been made. A number of
4 references have been made to the fact that in 1998, we're
5 very much like we were in 1987 with HIV. One of the things
6 I think we learned then is that as technology changes, it's
7 very difficult to develop long-term strategy protocols
8 because the technology changes, the drugs change.

9 Some of the most useful data we got at that
10 point was by establishing cohorts of patients that were
11 followed long term by saving specimens of serum and tissue
12 so that we could go back and relook at those populations
13 based on more sensitive assays, on different parameters
14 that we wanted to look at. So, I guess the only thing I
15 could add is I would hope that these cohorts are maintained
16 in a stable situation so they can be followed long term,
17 the specimens are kept so that assays that are more
18 sensitive or more specific or look at different parameters
19 can be reassessed in light of the natural history. I would
20 think that we would gain a lot of information that way.

21 DR. HAMMER: Thank you.

22 Just a few final thoughts. First, on behalf of
23 the committee, I'd like to thank the sponsor for a briefing
24 packet that was well put together and cohesive and for a
25 very cogent presentation today and responsiveness to the

1 questions.

2 I just have a few comments. Really I agree
3 with everything that has been said. As far as, just taking
4 some of these points in order, the post-marketing
5 information that's desirable in phase IV is clearly what
6 the long-term follow-up and durability is and the longer-
7 term safety. The question is how to get that. One can do
8 follow-ups from the trials, both controlled and
9 uncontrolled, and I would encourage that.

10 I think one of the pitfalls in these follow-ups
11 is that they tend to only follow the responders after a
12 treatment course is over or the study is closed. I would
13 suggest that we try to develop a way to look at responders
14 and nonresponders in the long term.

15 I would echo what Dr. Hamilton said about a
16 registry, and I think this is perhaps one of many instances
17 in which the agency can perhaps bring a number of sponsors
18 together who are developing agents for this disease to try
19 to enroll any patient in a study in a registry and in fact
20 talk about how that registry should be enlarged,
21 particularly at transplant centers that are seeing a lot of
22 patients and already have a transplant registry. The only
23 way really to ultimately find out what we're doing with the
24 longer-term outcomes of cirrhosis, cancer, transplant, and
25 death is going to be that way because no single study or

1 single sponsor I think will be able to answer that kind of
2 question.

3 As far as the special populations, they've been
4 well outlined. I would only one thing in relation to
5 decompensated liver disease. One of the new opportunities
6 we have, because the number of drugs are being developed of
7 the nucleoside and nucleotide class is in fact, once quick
8 early phase I/II studies are done with another new agent,
9 to determine the relative safety in a difficult situation
10 as has been done with lamivudine already. One can even
11 then begin to think about controlled trials in that
12 circumstance which to date have not been possible both
13 ethically and also because interferon is not tolerable in
14 that situation. But we will be able, in fact, to do
15 controlled trials in decompensated liver disease when we
16 have a number of agents that at least look relatively safe
17 early on.

18 As far as the issue of when to stop and when to
19 start, it's very difficult. I think some of the entry
20 criteria for the studies that were done here in phase III,
21 the higher risk patients clearly are the patients to treat,
22 and I don't think we can go too much beyond that at the
23 moment except for some of the compassionate sorts of uses
24 and pre-transplant uses that have been mentioned.

25 As far as when to stop, I think that's also